A STUDY OF THE HEREDITARY BASIS OF CLEFT LIP AND CLEFT PALATE

BY

Chester Tullio Coccia

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AUTHOR'S NOTE

The author used cleft lip and/or cleft palate to indicate the three entities of cleft lip, cleft lip and palate, and isolated cleft palate as has been noted consistently in the literature.

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INTRODUCTION

It is evident that medical progress has decreased the number of deaths due to congenital malformations over the years. Particularly noteworthy are those deformities of the head and neck which have succumbed to modern surgical techniques. These head and neck deformities vary in severity from the slightest anomaly, causing moderate disability with or without cosmetic inconvenience, to the most severe, which, without treatment would involve permanent disability or even death.

The congenital anomaly of cleft lip and cleft palate can be considered within the scope of this given definition. This affliction is quite a severe, disabling one. In the course of the past 30 years, however, the prognosis in the treatment of cleft lip and cleft palate has improved to such a degree that individuals so afflicted are able to live essentially normal lives with a minimal psychologic or cosmetic defect. The concept of the team approach to treatment, which encompasses both medical and paramedical disciplines, as well as speech therapy, has created an environment conducive to the solution of the problems of the cleft child.

Although numerous investigations of the etiology and pathogenesis of cleft lip and cleft palate have been reported, considerable disagreement persists.

As early as the 18th century, attention was given to the fact that heredity may be a prime factor causing cleft lip and cleft palate. Today, the general scientific consensus is that an hereditary disposition is an essential consideration. The primary problem which arises from this agreement is whether only a few, most, or perhaps all cleft palate cleft lip defects are hereditary in nature; if they are so considered, what is the manner of inheritance? Of the number of studies made, only a few have adequate statistical sampling. Various modes of inheritance were proposed ranging from simple recessivity to dominance with varying degrees of penetrance. Furthermore, since a large percentage of cleft lip with or without cleft palate patients do not demonstrate any simple Mendelian pattern of inheritance, many investigators believe that this type of congenital cleft may result from a complicated interaction between multiple genetic predispositions (polygenetic factors) and various ill-defined environmental factors. Stern[1] summarized what might be considered the present status concerning the etiology of cleft lip and cleft palate by stating that no phenotypic trait is independent of either hereditary or environmental agents, and an attempt to divide into two fractions, the inter-relation of two

agents, neither of which alone can produce a phenotype, is logically impossible.

During the last five years, the biochemical approach to the study of inherited diseases such as the hemoglobinopathies, has helped to precisely identify the affected gene being carried by an individual as well as the members of his family. An excellent example of such genetic identification is found in the disease of sickle cell anemia. The heterozygous "carriers" of the recessive genes causing this disease do not display any clinical pathologic symptoms. These individuals may, however, be identified by the fact that their red blood cells will show bizarre shapes under the influence of greatly reduced oxygen tension. The hemoglobin present in the sickled red blood cells are also electrophoretically abnormal. Thus, even the non-diseased, but gene carrier individuals, may be identified by the application of the correct criteria, reduced oxygen tension and electrophoresis. These carrier conditions, therefore, could be viewed as incomplete manifestations or "microforms" of the disease sickle cell anemia.

A sophisticated approach to the study of problems in human genetics will obviously be concerned with identifying in a population those individuals who carry a gene for a certain disease but who do not have

the disease for one reason or another. The reason for this approach stems from a fundamental principle of population genetics: most children affected by a relatively rare genetic disease (particularly recessive diseases) are born of normal, but "carrier", parents. The importance of identifying "unaffected" parents carrying the cleft lip-cleft palate genes becomes obvious.

In the case of cleft lip and cleft palate, there are various difficulties in determining a clear genetic hypothesis. Well documented laboratory studies have demonstrated that clefts can be induced in animals by changes in environmental factors and by the administration of teratogenic agents. Therefore, in some instances, the strong possibility exists that exogenous factors may be etiologic. In studies of families with an apparent genetic basis for the anomaly, the problem of complete and accurate records is a major one. Information obtained from vital records, such as birth and hospital records, is invariably neither complete nor accurate in detail. The value of the hospital record is dependent upon the interest and skill of the person who completed the source document. Family anamneses may also be of little value since the information given may often be inaccurate or completely

false. Finally, the families which display a definite genetic tendency do not appear to follow a specific mode of inheritance. One possible reason for this is the effect that environmental and other genetic factors may have on the penetrance and expressivity of the gene. This term, penetrance, refers to the presence or absence of the phenic trait for the given gene. In the case of cleft lip and cleft palate, the concept of penetrance is one which attempts to bridge the discrepancy between theoretical expectation on the basis of a genetic hypothesis and actual observation. This concept of penetrance, therefore, does not solve the problem, but rather poses it.

Microforms or incomplete manifestations may then result from either or both of two conditions: (1) the incomplete penetrance (or action) of the gene may be represented as minor anatomical discrepancies in the area of the lip and palate as a result of modification of the gene action due to environment or other genes present in the genome (haploid set of chromosomes) or, (2) these conditions may be the result of a heterozygous condition in which an individual may display minor anatomical discrepancies and at the same time be a "carrier" of the gene for cleft lip and cleft palate. In this case the problem is one of gene dosage. Therefore, the

purpose of this study is an attempt to identify a number of possible "microforms" and clarify their role in determining a manner of inheritance.

REVIEW OF THE LITERATURE

Due to the complexity of the problem of cleft lip and palate, the author decided that an examination of the literature in the following areas should be included in the scope of this thesis: (1) Embryologic development of the lip and palate; (2) Classification of the cleft lip and palate; (3) Epidemiological findings; (4) Proposed etiology of cleft lip and palate; (5) Associated anomalies noted with cleft lip and palate and (6) Proposed risk figures noted for reoccurrence of cleft lip and cleft palate.

I. Recent Embryological Studies

Development of the face and oral cavity begins during the second month of intra-uterine life.[2] In the differentiation of the face all three primary germ layers are involved. However, the ectodermal and mesodermal layers are the major components in the development of the lip and palate. The ectodermal layer gives rise to the epidermis and its associated structures (hair, sebaceous and sweat glands); Intra-orally, the epithelium, teeth, and taste buds of the tongue are also derived from the ectoderm.[2-5] Mesenchyme or embryonic connective tissue, which is of mesodermal origin, plays a determining role in the development of the lip and primary palate.[2-5]

After two or three weeks of embryonic development, several noticeable changes occur in the area of the embryonic face.[2] These changes can be grouped into two phases, the first of which concerns the foundation and preparation for the formation of the face. Initially, this includes the communication of the oral cavity with the foregut and the formation of the nasal ducts. In the terminal stages of this phase, the nasal and oral cavities are not separate entities but occupy one area. The development of the tongue has also occurred. In the second phase, the separation of the nasal and oral cavities occurs.[2] This separation is due to the development of the secondary palate.

Early development

The early development of the face begins at approximately 21-28 days in utero.[2-5] At this time the greater part of the face consists of a rounded prominence formed by the prosencephalon (forebrain). On the surface of this rounded prominence is a deep horizontal groove which will eventually become the stomodeum or the potential oral cavity. This depressed area is surrounded caudally by the mandibular arch, laterally by the maxillary processes, and cephalically by the frontonasal process. This stomodeal depression gradually deepens until its

floor makes contact with the endodeum of the foregut. Upon contact of the stomodeal ectoderm with the foregut endoderm a two layer epithelial membrane is formed: the buccopharyngeal membrane. Communication between the foregut and stomodeum occurs during the fourth week when the buccopharyngeal membranes rupture.[2-5]

The structures which surround the stomodeum are essentially the primordia from which the face is derived. These structures include the two mandibular processes, which unite early, the two maxillary processes, the lateral nasal processes, and the median nasal process.[2] The mandibular and maxillary processes are derived from the first branchial arch, whereas the two lateral nasal processes and the median nasal process, collectively designated the frontonasal process, originate from the forebrain.[2]

During the fourth week, the first significant change in the pattern of the face results from further development of the frontonasal process and its division into the median nasal and two lateral nasal processes. The lateral nasal and maxillary processes, which are adjacent to each other, are separated by a shallow groove (nasomaxillary groove). At this time, the stomodeum and nasal pits deepen and become more easily distinguishable.

Prior to the formation of the primary palate the median nasal process lags in its growth, thus allowing for the development of the globular processes. These processes represent a lateral rounding off of the lagging median nasal process. Therefore, differential growth of the lateral nasal, median nasal, and maxillary processes allow them to unite in the basic facial pattern.

Robinson[2] stated that the changes occurring in development of the middle face are due only in part to union of primarily separated processes. In most instances these processes are primarily united but are apparently separated by shallow grooves or pits; for this reason, he attributes most of the changes commonly considered as "fusions" to decreasing depth and disappearance of grooves or pits.

Development of the primary palate

There are two basic theories concerning the development of the primary palate -- the classical theory and the theory of mesodermal penetration.

The classical theory is based primarily upon the investigations of Dursy[6] and His[7] in 1869 and 1874, respectively. They maintained that there are five major "processes", or as Stark[8] described them, "peninsular masses of ectoderm and mesoderm" which develop about the

rim of the invaginated stomodeum.

His[7] outlined the formation of the middle face as follows:

> [The] midportion [of the face] is occupied by the oral cavity which is remarkably wide and angular. The ventral border is formed by the two maxillary processes. Above the mouth, the large expanse of the frontal process is found. Two clefts originate from the mouth on each side and end as blind pits. The first of these is the nasal cleft, which runs up into the frontal process and the maxillary process and terminates at the lens placode to become the naso-optic furrow. The lens of the eye develops from the lens placode. The naso-optic furrow remains open for some time, but eventually closes to form the nasolacrimal duct. These processes grow, meet and fuse. As a result of these fusions the nostrils, upper lip, and mandible are formed.

Embryologists continued to accept the classical theory until the early 20th century. Then, Pohlman,[9] in 1910, concluded from his investigations that the concept of fusion of the facial processes did not apply to the center of the face. More recent human embryologic studies by Veau and Politzer,[10] Stark,[8,11] and Tondury[12] strengthen Pohlman's concept of facial development and led to formation of the mesodermal proliferation concept.

The concept proposed by these men eliminates the recognition of individual facial processes. Instead, they recognized facial furrows which represent grooves

between the mesodermal masses underlying the ectoderm of the middle face. During the fifth and sixth week of intrauterine life the middle face is formed by differential growth mesenchyme and not by fusion of the facial processes (Figure 1). Stark[11] commented that the only place epithelial fusion normally occurs in the central face is at the lower border of the nasal pit. Furthermore, he noted that the concept of mesodermal proliferation and penetration applies only to the formation of the primary palate (lip, premaxilla, and alveolar process).

Today, most embryologists theorize that the development of the primary palate is accomplished by the mechanism of mesodermal penetration.[2, 8-12]

The tissue directly beneath the nasal pits but superior to the oral cavity represents the median nasal, lateral nasal, and maxillary processes which have reoriented and primarily united themselves near the midline.[11] This primary union represents the potential primary palate - the anlagen of the lip, premaxilla, and lower portion of the nose. In addition, this primary union reduces the size of the external opening of the nasal pits and converts them into blind ending sacs. Following the primary union of the facial

processes and the conversion of the nasal pits into blind ending sacs, the ectoderm between the nasal pits and oral cavity thickens and forms an epithelial wall. During this time of epithelial thickening, mesodermal penetration occurs and stabilizes the epithelial union of the facial processes.[11] However, at the blind end of the nasal pit, the epithelium becomes extremely narrow due to the differential growth occurring in the nasal pit area. Therefore, mesodermal penetration does not occur here and a nasobuccal membrane is formed.

Robinson[2] points out that during this period of differential growth and mesodermal penetration a change in the topographic relation of the nasal sac simultaneously occurs. This reorientation allows the nasobuccal membrane to separate the primitive oral cavity from the nasal sac. When this membrane ruptures, the nasal sac becomes a nasal duct leading from the nostril to the oral cavity, or as it is more commonly known, the primary choana (Figure 1). The mass of remaining tissue between the primitive nasal and oral cavities is the developing primary palate which becomes upper lip, premaxilla, and anterior alveolar process. Its integrity is established by six weeks of age.

Development of the secondary palate

Once the formation of the primary palate is complete, the development of the secondary palate begins.[2-11] The oral cavity at this time has an incomplete, horseshoe shaped roof which is formed anteriorly by the primary palate and laterally by the oral surface of the maxillary process. On the medial edge of the maxillary process two shelf-like structures are present. These structures represent the palatal processes which eventually grow downward and inward. These processes are blocked medially by the tongue which fills the oral cavity and has its dorsal surface resting against the inferior border of the nasal septum. However, through differential growth of the mandible, the tongue repositions itself downward and forward to allow for reorientation of the palatal processes. This reorientation encompasses the changing of the palatal shelves from a vertical to a horizontal position. They then fuse with each other and the nasal septum to form the secondary palate.

Peter,[13] in 1924, reviewed the embryology of the secondary palate in mammals and noted that the secondary palate was derived from two shelf-like projections which originated in the dorsolateral wall of the oral cavity. These projections extended downward and alongside the

tongue. When the shelves were eventually positioned dorsal (above) to the tongue, fusion occurred and the united halves formed the roof of the mouth. This fusion occurred first anteriorly behind the premaxilla, and progressed posteriorly to form the soft palate and uvula last.

Lazzaro,[14] in 1940, described various possible mechanisms to explain the sudden reorientation of the palate shelves. These were: (1) external forces such as muscular pressure by the tongue, (2) growth changes involving regression of the ventral portion and an outgrowth in the horizontal plane, and (3) a rapid rotation of the shelves due to some intrinsic force. Lazzaro, in his own work, favored the concept of rapid movement, and illustrated various cases of mammalian embryos with one shelf vertical and the other shelf horizontal as patterns of a rapid transitional stage in shelf rotation. He also noted a swelling in the shelves which he believed was due to an increase in intercellular substance of the embryonic connective tissue. In conclusion, Lazzaro acknowledged that release of the tongue's resistance must occur before the palatal shelves could "erect" or reorientate themselves. The proposed mechanisms of tongue movement were: (1) a lowering of the tongue and mandible,

(2) a forward displacement of the tongue, (3) a lifting of the roof of the oral cavity, (4) changes in form of the tongue due to muscular development, and (5) muscular movements of the tongue.

Walker and Fraser[15] demonstrated, both in fixed and in living mice embryos, a rapid movement of the palatal shelves from a vertical position lateral to the tongue to a horizontal position above the tongue. The change from a vertical to horizontal position appeared to start posteriorly by a bulging of the medial wall in and over the tongue and an accompanying retraction of the ventral portion of the shelf. This movement proceeded in a wavelike manner anteriorly until the whole shelf came to lie dorsal to the tongue. Force within the shelves appeared to be an important factor which at a given time allowed the palatal shelves to overcome the resistance of the tongue. There did not seem to be any active growth involved, but rather a sudden reorientation. In some instances, the wave of closure passed along one shelf more rapidly than the other, thus giving rise to the condition of one shelf being horizontal with the other still vertical. It was also observed that the general position of the tongue remained constant and that only its shape changed in response to the change in shelf

position. The side of the tongue adjacent to the vertical shelf was thick and compressed laterally, whereas the part of the tongue ventral to the horizontal shelf was more extended laterally and consequently not as thick. Evidence was also presented by these authors explaining the means by which the palatal shelves moved. The force for this supposedly was derived from a network of elastic fibers in the connective tissue of the shelves.

Stark,[8] in 1958, did not find any elastic fibers in his preparations of human embryo specimens.

Robinson[2] stated that the transposition of the palatal shelves occurs only when the tongue has moved down and thereby created a space between these processes. It has been proposed that the tongue movement is made possible by a sudden growth of the mandibular arch, both in width and length.

The results of a study involving the development of the palate in albino rats by Zeiler and associates[16] generally agree with that of Walker and Fraser.[15] However, Zeiler[16] found that the mandible did undergo a differential growth spurt prior to the time of palatal closure and fusion. A species difference noted was that in the mouse the medial margins of the shelves were almost straight and parallel, whereas in the albino rat the

shelves had a sinuous outline.

In considering the normal embryology of the lip and palate a relative time sequence of development must be considered. It is universally believed that the formation of the lip precedes the closure of the secondary palate.

Veau,[17] in 1934, examined 143 sections of normal human embryos and noted that the lip was fully developed by the seventh week. Arey,[4] Patten,[5] Bhaskar,[3] Robinson[2] and Stark,[8,11] agreed with this conclusion (Figure 2).

Millen,[18] in compiling a timetable of human development, suggested that all facial clefts close between 56 and 77 days after ovulation (Table I).

Fulton,[19] in a study of 88 human embryos found that the secondary palate fused at about the seventh week of the ovulation age or the ninth week following menstruation.

Woo[20] and Kraus[21] in studying a series of 84 and 151 human embryos and fetuses, respectively, found that after palatal fusion the structural interrelationships of the bony palate did not remain fixed throughout the prenatal period of growth. Kraus[21] described eight morphologic stages of development during which the bony palate reached its normal characteristic human proportions. He also concluded from various measurements, that, after fusion,

the palate grew by a rigidly controlled and highly complex pattern of differential growth.

Pathogenesis of cleft lip and palate

According to the classical view proposed by His[7] and Dursy,[6] cleft lip is a congenital malformation brought about by the failure of the embryo's normal morphological clefts to close. Therefore, failure of the facial processes (median, globular, and frontonasal) to grow, meet, and fuse can be considered the result of a developmental arrest.

Veau[16] and Fleishmann[22] completely disagreed with this idea. Their concept of the pathogenesis of cleft lip was that mesoderm failed to invade the potential cleft areas and support the delicate epithelial wall. This eventually led to the appearance of clefts of the upper lip and premaxilla, since the epithelial wall thinned out and pulled apart either partially or completely. The basis for this theory depended upon the clinical appearance of a web-like (Simonart's) band which frequently bridges the cleft area. Veau[16] believed that these bands represented the degenerating remnant of the epithelial wall penetrated incompletely by mesoderm.

Mauer and Hoepke[23] supported a modified form of the classical concept. They believed that mesodermal

penetration was an attempt to repair the existing cleft condition and not a normal developmental process.

Stark,[11] in a histologic study of five human embryos with cleft lip and cleft palate, found that the volume of mesoderm appearing in the area adjacent to the cleft was diminished or absent. He also theorized that the lip and premaxilla existed in their early forms as a single epithelial wall; within this wall of epithelium three masses of mesoderm were present.

The ratio of mesodermal and epithelial volume on the normal side of the primary palate would be 1:1. The finding of Simonart's bands or their remnants might suggest that if one mass of mesoderm were absent, the epithelium will pull apart and a cleft will result. The location of the cleft was thus dependent upon whether the missing mass was lateral or medial. If both lateral masses were missing a bilateral cleft of the lip occurred. From this study, Stark[11] also concluded that variance in mesodermal volume, even though no cleft resulted, may be the cause of some functional defects seen clinically.

Since the embryology of the hard and soft palate has been more completely studied, there is agreement among investigators that cleft palate arises from a lack of the palatal processes to coalesce.

Stark[11] noted in his cleft lip and palate embryos that even though the palatal cleft was present, the mesodermal volume in the region of the hard and soft palate was in a ratio of 1:1. He was of the opinion that this finding suggested and strengthened the "classical" theory of the fusion of the palatal processes.

In discussing the possible genetic and environmental factors involved in the etiology of cleft lip and palate, Fraser[24] postulated a number of possible events which may lead to the pathogenesis of the cleft palate:

(1) An interference with the build up of the shelf force may delay shelf movement sufficiently such that when the shelves reach the horizontal position, the head is too wide to allow contact of the shelves and the palate remains cleft. Fraser and his associates noted that in mice the cleft palates induced by maternal treatment with cortisone appeared to arise in this way.

(2) Palatal shelves that are too narrow to meet and fuse. Fitch[26] reported a recessive gene in a strain of mice which causes the palatal shelves to be too narrow even when they reach the horizontal position at the proper time.

(3) Excessive resistance of the tongue may also

delay shelf movement and thereby produced a cleft palate. Walker[27] produced cleft palate in mice by puncturing the amniotic sac of a mouse embryo just before normal palate closure. Fraser's explanation of this result was that the loss of the amniotic fluid caused a compression of the mandible against the chest wall. The tongue, in turn, was forced up between the palatal shelves, thereby delaying shelf movement.

(4) Excessive width of the head at the precise time when the palatal shelves fuse. Stark[8] believed that this factor may be an explanation for the reportedly high incidence of isolated cleft palate in patients with oxycephaly (a condition in which the skull is short and extremely wide due to the craniosynostosis of the coronal suture).

In a microscopic study of tissue sections, Avery and his associates[28] noticed in various human embryos, ranging in age from seven to 10 weeks prenatally, that the palate displayed considerable variation in structure between the normal and cleft lip and cleft palate embryos. The cause of abnormal palatal formation in the cleft embryos seemed to be defective cartilage development.

It has been proposed by numerous authors that, because of the sequential timing of lip development and

palatal closure, any disturbance of growth producing cleft lip could also affect the development of the palate. Furthermore, any disturbance of growth in the palate cannot affect the lip.[2-5,8,11] Fogh-Andersen[29] has presented data supporting this conjecture on the basis that in the case of cleft lip associated with cleft palate, both the right and the left cleft lip appeared less frequently than the bilateral cleft lip. Fogh-Andersen[29] theorized that since double harelip is more frequently combined with cleft palate than the single, it might to a certain extent be explained by assuming that cleft lip is the primary anomaly of development and cleft palate an associated secondary malformation.

II. Morphologic Classification of Cleft Lip and Palate

In describing the affliction of cleft lip and cleft palate, it is necessary to enumerate the anatomic variations which are seen in this malformation. The problem is not one of the cleft being present but one of description and classification. A wide variety of classifications are used by various authors, making comparisons among their data quite difficult if not impossible. It is evident that a continuum of clefts may be observed ranging from the slightest notching of the lip to the gross defect of a bilateral complete

cleft of lip and palate. If uniform classifications are not employed then it will obviously be impossible for various authors to do more than state results of their own study, omitting wider implications and failing to obtain independent confirmation by other investigators.

Davis and Ritchie,[30] in 1922, proposed an anatomic classification which used the alveolar process as the dividing line between clefts of the lip and palate. Thus, prealveolar clefts were assigned to Group I.; post-alveolar clefts to Group II., and complete alveolar clefts to Group III.. Furthermore, Group I. and III. were subdivided into unilateral, bilateral, and median clefts. Group II. clefts were subdivided according to involvement of the soft palate plus hard palate or soft palate only.

Davis and Ritchie[30] recognized that their classification excluded clefts of the palate and alveolus with a normal lip. Therefore, they suggested that all these should be grouped as post alveolar clefts. Upon presentation of this classification Davis and Ritchie[30] stressed its limitations and suggested that in some cases a complete anatomic description of the deformity must supplement the proposed classification.

Sherman,[31] in analyzing Davis and Ritchie's classification, utilized four groups which included clefts of

the lip without a concomitant palatal cleft.

Brophy,[32] in 1923, prepared a classification which included all the anatomic forms of cleft lip and palate. This classification consisted of 15 groups of which nine included clefts of the lip alone. Brophy felt that every muscle and bone involved in the deformity should be considered.

Veau,[33] in 1931, utilized a classification for four groups. Clefts of the lip alone were not included in this classification: Group I., clefts of the soft palate; Group II., clefts of the hard palate; Group III., complete unilateral clefts of lip, alveolus, and palate; and Group IV., bilateral clefts of the lip, alveolus, and palate.

Dorrance[34] proposed that only a verbal description of the severity and extensiveness of the cleft and not a numerical grouping was justifiable in classifying facial clefts.

In an hereditary study of cleft lip and palate Fogh-Andersen[29] emphasized the error of trying to correlate a phenotypic description based on a genetic hypothesis with a proposed surgical classification. Since a great number of the cases accumulated and grouped had undergone previous surgery, it was difficult or even

impossible to get the exact information on the original characteristics of the cleft. Therefore, for genetic purposes the following phenotypes were recognized: cleft lip, cleft lip associated with cleft palate, and isolated cleft palate.

A longitudinal growth study of 350 newborn infants with cleft lip or cleft palate was published by Pruzansky[35] in 1953. Cephalometric and laminographic radiographs along with study casts of the face and jaws, were used to classify the sample. Tabulated categories were based on the embryology, and physiology of the facial cleft. These categories included: (1) clefts involving the lip alone, (2) clefts involving the lip and palate, (3) those with the palate alone affected, and (4) congenitally short or insufficient palates.

Pruzansky[35] brought attention to the fact that he did not mention the alveolar process in his classification. He felt that by noting the extent to which the lip was involved, it was possible to accurately predict the extent of the cleft in the alveolar process. Although he acknowledged a direct relationship did exist between the extent of the defect in the lip and alveolar process he found it impossible to predict from the examination of the lip whether the palate itself was involved. This

finding can be explained by the temporally separate embryologic development of the primary and secondary palates. In the case of cleft lip with a cleft palate various degrees of incompleteness of the cleft in the lip and palate existed. Since a wide variation existed in this category, Pruzansky pointed out the necessity to use a supplemental anatomical description of the cleft in question.

Kernahan and Stark,[36] in 1958, suggested a classification dependent upon clinical findings and embryologic development. In this classification, the incisive foramen and not the alveolus was used as the dividing line between the different groups of facial deformities. The rationale behind this was based on the fact that the incisive foramen was the junctional point of development between the primary and secondary palate.

Motivated by the variance in the anatomy and severity of facial clefts, the nomenclature committee of the American Association for Cleft Palate Rehabilitation, in 1962 suggested a precise and complete classification for these clefts.[37]

The classification of maxillary cleft lip and palate was divided in two sections, the prepalate and

the palate. The prepalate, in turn, was divided into the lip and alveolar process up to the incisive foramen; the palate into the soft palate and the hard palate up to the incisive foramen. Under each of these subheadings provisions were made for location and extent as well as width of the cleft. Specific modifications were also noted; these included such factors as palatal attachment to the vomer, rotation and protrusion of the prepalate, submucous clefts, and congenital scarring of the lip. They also proposed that this classification would minimize any communication difficulties in describing clinical defects in terms of the involved parts of the cleft in question.

III. Epidemiologic Study of Cleft Lip and Palate

Frequency in the population

A wide range in occurrence of cleft lip and cleft palate has appeared in results of different investigations reported during the past 40 years.

In one of the first systematic studies to determine the frequency of congenital clefts, Davis,[38] in 1924, pointed out that one could not determine the incidence of congenital clefts from surgical records alone, since many of the children died at birth or were stillborn.

After an exhaustive study of archives and past histories, Sanders,[39] in 1934, noted that in the previous 40 years the prevalence of cleft lip and cleft palate had apparently increased. He believed that this apparent increase was due to a decrease in the number of childhood deaths which in turn would allow more of the affected children to marry and produce children who might also be affected. Krantz and Henderson,[40] Hixon,[41] Gentry and associates,[42] MacMahon and McKeown,[43] Ivy,[44] and Fogh-Andersen,[29,45] corroborated this finding in their investigations by noting a similar increase in the occurrence of this condition over the past two decades. Fogh-Andersen[29] believed that a study of birth registers as well as case records was necessary to determine the "natal frequency."

In discussing the reasons for increase in frequency of congenital clefts, Fogh-Andersen[45] suggested that the most likely explanation was that an increasing proportion of the population is obtaining surgical treatment for clefts. If one assumes a genetic basis for clefting, improved plastic surgery and rehabilitation methods would enable more persons affected with clefts to marry, reproduce, and hence expand the clefting genotype.

In reviewing the literature concerning the epidemiology of congenital clefts, Greene,[46] in 1963, emphasized that the number of cases of cleft lip and palate reported in the United States or any other country was actually an estimate based on isolated bits of information. This information was derived from various sources such as vital statistics, crippled children's registers, and hospital records. However, reports from a number of more complete studies provided some basis for speculating about the cleft lip and palate prevalence in the United States.[44,48,52,57,73] Furthermore, the data from these studies provided an estimate of 1.3 cleft births for every 1,000 live births. In using this gross estimate together with a birth rate of 24.1 per 1,000 per year and the 1960 population figure of 179.3 million from the U. S. Bureau of the Census, Greene[46] estimated that nearly 6,000 new lip and palatal clefts births occurred each year in the United States.

Considerable variation has been noted in morbidity rates. Sanders[39] found that 8.3 percent of the affected children died within the first year; of these 3.5 percent were stillborn. On the other hand, Fogh-Andersen[29] found that nine percent of the affected children were

stillborn and that 12 percent died within the first 10 days. Van der Woude's[47] study showed that eight percent of the affected children died within the first month. Loretz, Westmoreland, and Richards[48] noted that 15.5 percent of the affected children died within the first six months.

Greene[46] claimed that variation in the data may be explained by the apparent increase in case sources, completeness of case findings, criteria for selecting cases, sample size, and decreased perinatal mortality.

Distribution of cases by sex and type of cleft

The distribution of cases by sex and by the type of cleft has been recorded in a number of studies.

In examining the histories of cases accumulated over a period of 60 years, Haug,[49] in 1904, commented on the incidence of facial clefts in relation to the sex of the individual. He found that cleft lip and palate occurred twice as often in males. This 2:1 ratio was also noted in the investigations of Birkenfeld,[50] 1926; Sanders,[39] 1934; Fortyn,[51] 1936; Grace,[52] 1942; and Loretz,[48] 1961.

Birkenfeld[50] reported a 1:1:2 ratio in the frequency of clift lip, isolated cleft palate, and cleft lip with cleft palate, respectively. These figures were

not related to sex. In 1942, Fogh-Andersen[29] observed the same ratio of occurrence of these morphologic types.

In contrast, the data accumulated by Fraser and Baxter,[53] Mazaheri,[54] MacMahon and McKeown,[43] and Fraser and Calnan[55] did not completely agree with the 1:1:2 ratio. Fraser and Baxter,[53] and Mazaheri[54] found a very small number of cases with isolated cleft lip, whereas, MacMahon and McKeown[43] and Fraser and Calnan[55] reported an unusually high proportion of isolated cleft palate cases. No explanation was given for these differences.

Test and Falls[59] studied a five generation pedigree and noted that their findings completely disagreed with the 1:1:2 ratio. In fact, the total affected offspring of the affected parents displayed a slight preponderance of females to males.

In analyzing the prevalence of each morphological cleft, Fogh-Andersen[29] demonstrated that isolated cleft palate occurred more frequently among females. The studies of Hixon,[41] Fraser and Calnan,[55] MacMahon and McKeown,[43] Fraser and Baxter,[53] Mazaheri,[54] Woolf, Woolf, and Broadbent,[56] Greene, Vermillion, Hoy, Gibbens, and Kerschbaum,[57] and Curtis[58] agreed with this finding.

It should be noted that in the most recent

studies,[41,43,54-57] the information regarding the distribution of cases by sex and type of cleft deformity, regardless of ratio, tend to agree on several points: (1) cleft lip and cleft palate occur more frequently together than separately; (2) clefts of the lip with or without associated clefts of the palate are more common in the male than in the female; (3) isolated cleft palate is more common in the female; and (4) considering all morphologic clefts of the lip and palate together, males are more frequently affected.

Many investigators noticed a preponderance of left-sided lip clefts. Haug's[49] material showed a ratio of 2:1:1 for the occurrence of the left, right, and bilateral clefts. The more severe cases were more common in the male.

Davis[38] discovered that the left-sided and bilateral cleft lip occurred with equal frequency, each being about twice as frequent as the right-sided cleft lip.

In contract to Davis's data, Fogh-Andersen[29] found that the cleft lip appeared most frequently on the left side, secondly, on the right side, and least often bilaterally. In the case where cleft lip was associated with cleft palate, the lip cleft was likewise found more often on the left; however, either the

left or right cleft was associated with cleft palate less frequently than the bilateral cleft lip. The more severe cases of isolated cleft palate were found in females, whereas the more severe cases of cleft lip with or without cleft palate were found in males. Fraser and Calnan,[55] Sesgin and tark,[60] and Greene and his associates[57] found this to be true in their investigations. No satisfactory explanation for this phenomena has appeared in the literature.

Incidence based on race

There are only a few well-documented studies which mention the frequency of facial clefts according to race.

Davis,[38] reported that only seven clefts were observed among 12,520 Negro births (.55/1000 live births), while during the same period there were 17 cases among 15,520 births of white children (1.06/1000 live births).

Grace,[52] observed that 5.6 percent of the children born in 1942 were Negroes, whereas, only 3.6 percent of those born with clefts were Negroes. It was also noted that the frequency of cleft lip with or without cleft palate was much greater in Caucasians.

Ivy[44] made a similar investigation in 1961 and found that one in 753 live white births was born with cleft lip and/or cleft palate. According to these

figures the frequency of cleft lip with or without cleft palate is about five times greater in whites than in Negroes.

Krantz and Henderson[40] studied the frequency of cleft cases in relation to maternal ancestry. They noted that children of Filipino mothers who were a blend of the black, brown, yellow, and white races had a significantly higher rate of clefting (3.5/1000 live births) than did children born to Caucasian mothers (.5/1000 live births). However, these rates were estimated from a limited sample.

Lutz and Moor[61] reported on 303 cleft cases among births in the Los Angeles County General Hospital. By race, the cleft case rates per 1,000 live births were: Caucasian 1.00; Mexican 1.25; and Negro 0.71.

Bender, Coe, Baakladt, and Houle,[62] in 1956, found that only one of 433 cleft lip and palate cases in their sample was that of the Negroid race.

Loretz and his associates[48] found that the clefting frequency in various races in California differed greatly. In 1955, 6.9 percent of all births were Negroes, but only 3.5 percent of the children born with clefts were Negroes.

Neel,[63] in 1958, made a study of congenital

defects in Japanese infants. The data which was acquired made it possible to compare Caucasian, Negro, and Mongolian populations. It was demonstrated that cleft lip and palate occurred more frequently in Japanese than in Caucasian populations, and more frequently in Caucasian than in Negro populations. In the Japanese, cleft lip and palate appeared more frequently in conjunction with other congenital malformations than as a single defect.

Sesgin and Stark,[60] in 1961, discovered that the total number of congenital defects in their sample apparently was much greater in the white newborn babies (67 percent) as compared to the pigmented newborn (33 percent). Cleft lip and/or palate frequency was reported to be low in the Negro.

Tretsven[64] studied the frequency of cleft lip and palate in Montana Indians. He found that cleft lip and palate occurred twice as frequently in these Indians as in the surrounding Caucasian population. The incidence of clefts was one to 276 live births. This high frequency was attributed to the large number of consanguineous marriages. On the other hand Greene and his associates[57] showed certain American Indian tribes to have a much lower rate (121/100,000), although these observations

were based on a limited sample.

In an epidemiological study of cleft lip and palate in four states, Greene and his associates[57] noted that Negroes had the lowest incidence of facial clefts (1:1,821) and Japanese the highest (1:674).

In a review of the literature by Greene,[46] it was stated that even though these studies concerning influence of racial factors in clefting were made on select populations, they strongly suggest that there are real differences in prevalence among the races. However, these differences may be due to concomitant environmental influences rather than racial factors.

Incidence based on parental age and birth rank

Numerous reports have appeared in the literature both denying and supporting an association of parental age and birth rank with the frequency of clefts.

In Davis's[38] investigations 54 percent of the births with congenital clefts were primipara.

Grace,[52] 1942 and Beder and associates,[62] 1958, concluded that mothers between the ages of 19 and 24 gave birth to more babies with clefts than did mothers of other age groups. Beder's[62] conclusions were questioned by Greene[46] since the data presented was based

on counts of cases rather than on age-specific prevalence rates. Grace's[52] survey also disclosed that 41.6 percent of her sample of 250 were primiparous.

In analyzing the relationship between parental age, clefts, and the type of cleft, Fogh-Andersen[29] could find no significant relationship. He compared the mean age of the mothers of children with clefts with the mean age of all Danish women who gave birth to a child in a single year. A similar procedure was followed when considering paternal age. No association was found between the occurrence of cleft lip and/or palate and birth rank.

McEvitt[65] compared the age of parents of 282 infants born with clefts with the parents of 7,927 normal births. No relationship between parental age and frequency of cleft formation was noted. The relationship of birth rank to the incidence of these clefts was also found to be insignificant.

A statistically significant relationship between cleft lip and palate with maternal age was reported by MacMahon and McKeown,[43] in 1953, and Woolf, Woolf, and Broadbent,[56] in 1963. Interestingly, they also found no relationship between isolated cleft palate and maternal age. Also, no correlation was noted between

birth rank and cleft lip and/or palate frequency.

Fraser and Calnan[55] postulated that advanced maternal age in primipara may predispose to cleft lip in girls and cause a more severe combined cleft lip and palate in boys. An increase in paternal age was found to be associated with cleft lip and palate infants. It was suggested that paternal mutation in later life may be involved in the pathogenesis of this condition.

The investigation of Peer, Strean, Walker, Bernhard and Beck[66] concluded that there was no relationship between the frequency of clefts and parental age. However, no supporting data was presented.

Mazaheri[54] offered five observations regarding birth rank and parental age drawn from his data. They were summarized as follows: (1) No significant relationship was discovered between differences in age of husband and wife and the frequency of birth of children with cleft lip and/or cleft palate, as compared to normal children; (2) A significantly increased probability for the birth of a child with cleft lip and/or palate with increasing age of the mother; (3) A significant relationship between birth rank and the probability of the birth of cleft lip and/or palate child. Cleft lip and/or palate children occurred more

frequently in the later birth ranks, and less often in the earliest birth ranks than would be expected by chance. (4) The first born of older mothers were cleft twice as frequently as were the first born of young mothers; (5) No comparable relationship was found between the age of fathers and the frequency of births of cleft lip and/or palate offspring.

Rank and Thomson's[67] investigation demonstrated a higher incidence of cleft lip and/or palate babies born to older mothers. It was suggested that the effect of birth rank may be related to or altered by this factor.

Loretz and his associates[48] and Phair[68] learned that the percentage of infants with cleft lip and/or palate born to mothers 35 years of age and older was significantly higher than the percentage of children so affected born to mothers under 35 years of age.

A comparison between the incidence of clefts of the lip and palate in families with children with clefts and families without clefts was made by Spriesterbach and his associates[69] in 1962. Intragroup differences in the family history reports from these two groups were also investigated. From this intragroup investigation Spriesterbach found no significant relationship between the incidence of the cleft lip group, cleft lip and palate group, or the cleft palate group as to maternal

age.

Tretsven[64] reported that 85 percent of the Montana Indian babies born with clefts were within the three to five birth rank range, whereas the non-Indian babies were of the one to three birth rank range. The Indian mothers bearing these cleft children were also older than the mothers of the non-Indian infants with clefts.

Fujino, Tanaka, and Sanui,[170] in 1963, studied 2,828 Japanese cases with clefts. His data showed a significantly higher number of cleft lip and palate births occurring in the family's fifth or later birth.

Greene and his associates[57] demonstrated that a positive relationship existed between the advancing age of parents and the frequency of clefts, but birth order was not related to the occurrence of clefts.

Incidence based on geographical distribution

After an extensive review of the literature, the author has noted that very little information is available on the geographic distribution of cases of congenital clefts.

Davis[38] examined World War I draftee records and found a difference in the frequency of congenital clefts around the country. Vermont was the highest with 1.55/1,000 and Arkansas the lowest with .16/1,000.

These figures were not deemed conclusive since the data was based on place of residence and not necessarily place of birth.

Fogh-Andersen,[29] Hixon,[41] Curtis,[58] and Curtis and Walker[71] found no correlation between geographical location and the frequency of congenital clefts.

A study in Hawaii by Henderson[72] reported 1.98 cleft cases per 1,000 live births. This attack rate, the highest reported in the Unit d States, probably is influenced by Hawaii's mandatory reporting system which has been in effect since 1938. Kratz and Henderson[40] attributed a large portion of the excess of clefts in Hawaii to the high case rate among the Filipinos.

Many investigators[44,48,52,56,57,73] in the United States have reported rates for their area, but lack of comparability prevents the formulation of meaningful conclusions. Since it has been demonstrated that the occurrence of cleft lip and/or palate in the three major racial stocks (Caucasion, Negroid, and Mongoloid) is considerably different, any geographic study must necessarily take this important variable into account.

Incidence based on seasonal distribution

Lutz and Moor[61] found that among 303 children

with clefts born in Los Angeles between 1936 and 1951, more children with clefts were born during June, July, and August than in any other quarter. The seasonal distribution of normal births was not described.

Stevenson, Worcester and Rice[74] reviewed obstetrical records of mothers who gave birth to malformed infants in Boston between the years 1930 and 1941; 34 of 677 malformed children had clefts. Most of these children were conceived in the first and fourth quarter. No explanation was given for this phenomena.

Phair,[68] Fraser and Calnan,[55] Woolf, Woolf, and Broadbent,[56] and Greene and his associates,[57] found no unusual seasonal variation in the frequency of congenital clefts while the Japanese study of Fujino, Tanaka and Sanui[70] noted that the percentages of subjects with cleft lip and palate were highest among those born in spring (March to May) and lowest among those born in summer and fall.

It should be apparent that any study of seasonal distribution of cleft is without meaning unless compared to the seasonal distribution of normal, live births of that same general population.

IV. Congenital Anomalies Occurring with Cleft Lip and Palate

In much of the current literature the anomaly of

cleft lip and cleft palate was studied as part of a group with many of the other congenital defects.

Davis[38] and Birkenfeld[50] found that 25 to 31.5 percent of the cases had associated anomalies. These anomalies varied from neurological disturbances to defects of the extremities. Birkenfeld[50] postulated that this occurrence of associated anomalies could be attributed to a possible coupling of the genes.

Ten percent of the cases studied by Fogh-Andersen[29] presented associated anomalies; however, he claimed that the "normal" frequency of these malformations hardly exceeded one percent.

Sesgin and Stark[60] also found a 10 percent frequency of associated anomalies with cases of cleft lip and/or cleft palate.

Curtis[58] noticed that the significant number of associated anomalies that was found in both groups (isolated cleft palate and cleft lip with or without cleft palate) varied greatly. Fourteen percent of the cases with cleft lip and cleft palate had associated anomalies, whereas 32.9 percent of the cases with isolated cleft palate displayed associated anomalies. Curtis[58] felt that the associated anomalies such as mongolism and congenital heart disease were one part

of a generalized disturbance in development.

In separating their cases into three categories, Beder and his associates[62] found the following percentages with associated anomalies: cleft palate, 25 percent; cleft lip and palate, 12 percent; and cleft lip, seven percent.

A similar study by MacMahon and McKeown[43] demonstrated a 14.9 percent occurrence of associated anomalies with cleft palate, 9.1 percent association with cleft palate, and a 21 percent association with cleft lip and cleft palate.

The California study by Loretz and his associates[48] indicated that of the 127 malformations associated with cleft lip and cleft palate 36 percent involved the skeletal system; 22 percent, the nervous system; 10 percent, the genito-urinary system; five percent, the gastrointestinal system; three percent, the circulatory system; and 23 percent, other systems.

In discussing cleft lip and cleft palate, Neel[63] noted that the multiple defect involving the central nervous system occurred with cleft lip and/or cleft palate in 39 percent of the Japanese cases as to the 13 percent found in Caucasians. Generally speaking, the preponderance of cleft lip and/or palate in

Japanese appeared greater in multiple malformations than as a single malformation.

Fraser and Calnan,[55] Curtis and Walker,[71] and Greene and his associates[57] agreed with Curtis'[58] study that associated anomalies appeared more frequently with isolated cleft palate than with cleft lip and cleft palate. Curtis and Walker[71] found that 18.4 percent of the isolated cleft palates displayed associated anomalies. Furthermore, Fraser and Calnan[55] did not give a specific figure relating to the frequency of associated anomalies with isolated cleft palate; they did note that a large number of the associated anomalies present were the Pierre-Robin syndrome.

In seeking a positive relationship between the occurrence of facial clefts and other selected congenital malformations, Greene and his associates[57] suggested that the published figures of nine to 21 percent represents the minimum frequency with which clefts are actually associated with other congenital malformations. This suggestion was based on the fact that many developmental defects of the newborn are difficult to detect.

A study of 60 aborted embryos and fetuses with

cleft lip and cleft palate by Kraus and his associates[75] determined that more than half (61.7 percent) had associated malformations. This was in strong contrast to the highest incidence of associated malformations (25-31.5 percent) as previously reported.[38,50]

According to various investigations,[29,48,57] the more common anomalies are: syndactylism, spina bifida, clubfoot, polydactylism, congenital heart disease, mental retardation, malformed ears, and micrognathia.

V. Etiologic Factors

Heredity

Over the years much attention has been focused on the role of heredity in congenital malformations. Fundamentally, this role has been investigated along three facets: pedigrees or histories of the anomaly in family groups, twin studies and mode of inheritance.

Pedigrees of families with congenital clefts were studied as early as 1757.[76] Between the years of 1794 and 1865 a large amount of data concerning individual families with cleft formations was published.[77-80]

In more recent studies, familial occurrence in a great number of pedigrees demonstrated that congenital clefts could possibly be attributed to multiple genetic

factors. Haug,[49] Davis,[38] and Rischbieth[81] noted this. However, no attempt was made to discuss the manner of inheritance.

The pedigree studies of many investigators[24,29,39,55,58,60,63,67,82-85] generally agreed that the manner of inheritance involved at least two main genetic complexes; that for cleft lip with or without cleft palate and isolated cleft palate. Some authors believed that the difference in sex distribution was a major factor in determining these genetic complexes. Birkenfeld[50] found a preponderance of cases which displayed sex linkage.

Schroder[82-84] concluded that some of the pedigrees he studied displayed a combination of recessiveness and sex-linkage.

On the basis of sex distribution alone (twice as many affected males as females), Fortuyn,[51] 1936, proposed that the manner of inheritance may be that of double recessivity with one gene on an autosomal chromosome and the other gene on the sex chromosome.

These conclusions were reached in an analysis of data provided by Birkenfeld,[50] Schroder,[82-84] and Cunningham.[86] However, Cotterman and Synder,[87] 1937, and Cisk and Mather,[88] 1938, completely disputed

Fortuyn's[51] theory. Cotterman and Synder[87] pointed out that even if the manner of inheritance was that of double recessivity with one autosomal and one sex-linked gene, ratio of males to females need not be 2:1. In obtaining a "sibship analysis" of the material, Cisk and Mather[88] concluded that the manner of inheritance was not attributable to sex linkage. This conclusion was based on the difference of the incidence of the character among the brothers and sisters of the male and female propositi in reports of Sanders[39] and Schroder.[82-84]

Analyzing Schroder's[82-84] and Sanders's[39] data for sex-linkage, Mather and Philip,[89] in 1940, discovered two different modes of inheritance. Sanders'[39] pedigrees displayed complete autosomal inheritance, whereas, in a number of cases, Schroder's[82-84] showed partial sex-linkage. Therefore, in this material, a minimum of two different genes, one autosomal recessive and one sex-linked recessive, governed the incidence of cleft lip and cleft palate.

Analyzing his own material, Sanders[39] believed that five hereditary factors determine the malformation, cleft lip and cleft palate. These five factors were based on which side of the lip the cleft appeared as

well as the severity of the cleft. Therefore, the manner of inheritance was attributed to polymerous recessive factors and not sex linkage or sex limitation. Hantzchel[85] agreed with Sanders[39] as to the possibility of polymeric recessiveness.

In 1942, Fogh-Andersen[29] compiled an extensive report on the inheritance of cleft lip and cleft palate. In orienting and classifying his material, Fogh-Andersen[29] concluded that on a genetic basis there were only two mutually independent malformations: cleft lip with or without associated cleft palate and isolated cleft palate. In cleft lip with or without cleft palate, the manner of inheritance was found to be that of "conditioned dominance" with sex-limitation to males. However, in the case of isolated cleft palate the manner of inheritance seemed to be that of simple dominance with "failing manifestation" and sex limitation to females.

Fraser[24] studied the influence of genetic factors on experimental cleft palate caused by maternal treatment of mice with cortisone. Variation in results obtained with different strains of mice demonstrated that cleft palate in mice was due to numerous mutant genes. Since he believed that mutant genes were also

the cause of cleft palate in humans, Fraser[24] compared his results with those in humans. The mice data resembled the human affection in t at cleft palate alone was genetically different from that of cleft lip with or without cleft palate. These findings supported Fogh-Andersen's observations.

Curtis,[58] Hixon,[41] and Rank and Thomson[67] did not agree with Fogh-Andersen's conclusion that cleft lip with or without cleft palate was occasioned in all instances by a genetic system independent of that producing cleft palate alone. However, they did agree that the manner of inheritance was due to multifactorial genetic conditions.

Rank and Thomson[67] also believed that these genes were dominant, autosomal, and of reduced manifestation.

The repeated observation that an excess of males have cleft lip with or without cleft palate suggested to Fraser and Calnan[55] that infant girls were less susceptible to the interactions of polyfactorial, genetic, and environmental factors which were concerned in the pathogenesis of this malformation.

Curtis and Walker[71] stated that the anomaly of cleft lip with or without cleft palate was due to at least two pairs of recessive genes. In the case of

isolated cleft palate, Fogh-Andersen's theory of simple dominant inheritance with greatly reduced penetrance was supported.

Fogh-Andersen[29] compared the frequency of clefts among the relatives of the propositi and among the general population. There was a significant difference between the frequency of cleft lip with or without cleft palate in the total population; the same condition appeared among siblings, parents, and the parent's sibs of individuals with cleft lip and/or cleft palate. Furthermore, a significant difference was noted in the frequency of occurrence of isolated cleft palate in the total population and among siblings of the isolated cleft palate proband. He proposed that this data strongly suggested heredity factors to be important in the etiology of these facial clefts.

Investigation by Schwartz,[90] Stiegler and Berry,[91] and Peer and his associates[66] demonstrated families with multiple occurrences in varying percentages. However, the data of Peer, Strean, Walker, Bernhard and Beck[66] was of limited value since only families of children with repaired clefts were used.

Fraser and Baxter's[53] investigation of the distribution of clefts observed among 70 families demonstrating cleft lip and palate demonstrated a significant

difference in the prevalance between cleft lip and/or palate and isolated cleft palate cases. This tends to support Fogh-Andersen's[29] findings.

Spriesterbach and his associates[69] studied family health histories from parents of 111 children with cleft lip or palate and from 175 parents whose children did not have any facial clefts. In comparing the index and control groups, it was noted that the index group had 17 times more relatives with cleft lip and palate than the control group (105-10,000; 6-10,000).

The families of isolated cleft palate patients had a higher incidence of associated anomalies and a lower number of counted relatives with clefts than did the families of the patient with cleft lip or cleft lip with cleft palate. The authors felt that this evidence suggested either a different hereditary pattern for the two conditions or that more severe pregnancy events may tend to produce more clefts of the palate only as to clefts of the lip or lip and palate combined.

Fujino and his associates[70] demonstrated that among 2,792 siblings of cleft lip propositi, 33 (1.8 percent) had cleft lip and 13 (.47 percent) had cleft lip and palate; none had cleft palate alone. It was also noted that the incidence of cleft lip among

brothers of cleft lip propositi was higher than among the sisters. A similar excess of brothers with cleft lip was noted among the siblings of propositi with cleft lip and palate. There was also an extremely high number of consanguineous marriages in which both parents were normal, resulting in offspring with clefts.

The combined rates of siblings with cleft lip or cleft lip and palate was 10 times higher than the rate of subjects with such clefts in the general Japanese population. There was no conclusion as to the mode of inheritance. However, it was pointed out that these data did demonstrate a definite genetic trend.

Twin studies by Birkenfeld,[50] Idelberger and Idelberger,[92] Fogh-Andersen,[29] Curtis,[58] Metrakos and Metrakos,[93] and Douglas[94] have shown some degree of concordance among monzygotic twins. Since the amount of data was limited, no definite conclusions as to the manner of inheritance were reached. However, many of the cases presented the possibility that hereditary factors played an important role in the etiology of cleft lip and cleft palate.

On the basis of twin studies, Curtis[58] disagreed with Fogh-Andersen's[29] conclusion that a pedigree with isolated cleft palate will not show a child with cleft

lip and vice versa.

Douglas's[94] review of 30 monozygotic and 70 dizygotic twins, in 1958, demonstrated a 30 percent concordance of monozygotic twins compared to 5.4 percent between dizygotic twins. The author felt that these results emphasized the role of genetic factors in cleft formation.

It should also be noted that in these studies many methods of determining zygosity were discussed and presented. This is an essential factor to consider in order to obtain meaningful results.

The influence of environmental factors and teratogenic agents

In reviewing the role of heredity in the occurrence of cleft lip and cleft palate, it was seen that no definite conclusions were reached even though extensive studies have been made over the past 25 years. Most authors agree that the anomaly of cleft lip and cleft palate seems to be due to a complex interaction of multifactorial genetic and environmental conditions. Approximately 20 percent of the material accumulated displayed a familial disposition. From this 20 percent, various modes of inheritance were deduced. However, 80 percent of the data did not display a definite pattern of in-

heritance. Various environmental factors as well as teratogenic agents have been considered to be associated with this anomaly. However, with better diagnostic facilities and with more complete records this figure may be considerably reduced.

In a study of glaciated and non-glaciated areas, Brown,[95] in 1939, reported that thyroid deficiency was a possible teratogenic agent of congenital clefts. Henderson,[72] in 1940, after completing a similar study, denied this observation on the basis that she could not find any correlation between hypothyroidism and congenital clefts.

Davis[38] and Campbell[96] found congenital syphilis to be present in many of the congenital cleft cases which were discussed. However, no definite conclusions were reached as to the role of syphilis in the etiology of cleft lip and palate.

Gregg,[97] Prendergast,[98] Swan and Tostevin,[99] Patrick,[100] and Brawner[101] have presented a number of cleft lip and/or palate cases which were associated with maternal rubella. The observed frequency of isolated cleft palate was greater than that of cleft lip and palate. These investigations of rubella and congenital malformations suggested that cleft palate

occasionally might be associated with a viral infection.

Fraser[24,102,103] found that the treatment of pregnant mice with cortisone acetate increased the incidence of cleft palate. However, it was found that this teratogenic agent influenced the genetic factor regulating palatal closure in various strains of mice. It was also demonstrated that both the maternal and foetal genotypes were important in determining the embryo's response to the teratogen.

Isaacson and Chaudhry,[104] Ingalls and Curley,[105] and Woolan and Millen[106] have substantiated Fraser's findings. Ingalls and Curley[105] using hydrocortisone and Woolan and Millen[106] using cortisone increased the expression of cleft palate produced by hypervitaminosis A.

Strean and Peer,[107] in a retrospective study of maternal case histories, revealed a high incidence of physiologic, emotional, or traumatic stress during the first trimester of pregnancy. Fraser[24] questioned this finding since this data was acquired solely through maternal memory. He felt that maternal memory bias is a source of error and is most difficult to control since a mother of an abnormal child is more likely to remember

unusual events during the pregnancy than will the mother of a normal child.

Nutritional deficiencies also have been associated with the occurrence of cleft palate. Asling[108] found that a deficiency of pteroylglutamic acid (folic acid) in pregnant rats produced cleft palate and in most cases micrognathia.

Peer and his associates[109] found that the administration of Vitamin B_6 and folic acid in various combinations decreased the incidence of cleft palate in pregnant mice which were injected with cortisone acetate.

Conway[112] and Peer and his associates[66] found that supplemental vitamin therapy (B complex, multiple vitamins, and folic acid) given to pregnant women who already had children with cleft lip and/or cleft palate seemed to reduce the incidence of the anomaly. However, the study was too small to reach any definite conclusions.

Douglas[110] contended that vomiting during pregnancy caused depletion of certain essential elements during the first trimester of pregnancy. He theorized that this depletion may have some affect on the developing lip and palate.

McGainty and his associates[111] noted that less

than 15 percent of pregnant women see an obstretrician before the first trimester is over. Therefore, dietary supplements are not given when they are most needed.

Pinsky and Fraser[113] found that short term exposure of mice to the teratogenic agent 6-aminonicotinamide, caused cleft lip and hind limb malformations.

Warkany[114-116] in his research with experimental animals produced a higher number of clefts by subjecting pregnant animals to X irradiation, Vitamin A deficiency, riboflavin deficiency, pantothenic acid deficiency, and folic acid deficient diets, alone or in combination with vitamin antagonists; cortisone, compound F, and ACTH injections; low atmospheric pressure; nitrogen mustard injections; and hypervitaminosis A.

Erdelyi[117] believed that toxoplasmosis passing through the diplacental route with maternal blood may be an exogenous agent causing cleft lip and cleft palate.

According to Buchner[118] the four principle environmental causes of non-inherited facial clefts were acute virus infections, avitaminosis, oxygen, and glucose deprivation of the mother.

Feild, Kreshover and Lieberman[119] noted that the

effects of temporary anoxia upon the fetal tissues of mice resulted in an increase in fetal morbidity and in the number of congenital malformations. The greatest frequency of deformities occurred after a 45-minute vascular occlusion on the 15th day. There were 13 instances of palatal clefts, eight of which occurred in young subjected to anoxia on the 14th day.

Possible incomplete manifestations or "microforms" of cleft lip and palate

Although there is voluminous literature regarding cleft lip and palate, the possible genetic carriers of cleft lip and/or cleft palate have not been identified. One investigator[120] has suggested that subjects with "microforms", which represent the lightest degrees of the manifestation, may be possible genic carriers. On the other hand, these "microforms" may be a result solely of genic action which is completely free from the influence of other factors such as environment. Therefore, the manifestation present is a limited or masked one. These "microforms" may also be a result of incomplete penetrance of the gene, which again may be determined by factors such as environment and teratogenic agents.

Fogh-Andersen[29] noted in most cases of cleft lip, even without a visible cleft in the alveolus, there

was an irregularity of the involved incisor or the cuspid. In some instances supernumerary teeth in this area may also be present. It was further mentioned that the study of Lucas,[121] in 1888, called attention to the fact that in relatives of the propositi these dental anomalies occurred quite frequently without an associated cleft of the lip and palate.

Mengele,[122] in 1939, mentioned other anomalies which could be considered as "microforms" of cleft lip and palate: a high, narrow arched palate, submucous cleft palate without a visible anomaly, notching of the upper lip, and bifid uvula.

In 1928, Davis[123] reported that 57 percent of his cleft patients had a positive familial history. His criteria for a positive family history included not only cases of the lip, face, and palate, but also those with congenital absence of the maxillary lateral incisors or those with maxillary supernumerary teeth.

Bohn's[124] investigation of dental anomalies occurring with cleft lip and/or cleft palate noted that the more severly affected cleft lips usually had a tendency for hypodontia in the secondary dentition as well as smaller teeth in the maxillary

anterior region.

Olin,[125] in 1964, observed that all patients with cleft lip only or cleft lip and palate had some degree of deformity of the anterior teeth in the area of the cleft. The incidence of missing bicuspids in these patients was also extremely high (24 percent).

The association of congenital mandibular lip pits with cleft lip and palate has been demonstrated by various investigators.

Van der Woude[47] concluded that the congenital anomaly of mandibular lip pits was due to a single dominant gene. However, its effects may vary from the full triad of cleft lip, palate, and lip pits to a condition in which no detectable manifestations are noted. She also observed no evidence of sex-linkage, sex-limitation, or sex influence. It was also noted that the variable penetrance of this hypothetical gene allowed the trait to be transmitted by an apparently normal person. Furthermore, severely affected parents with the triad tend to have more severely affected offspring, in comparison to mildly affected parents.

The investigation of Curtis and Walker[71] presented nine families showing an association of cleft lip and

palate with lip pits. The pedigrees of these families tended to support Van der Woude's conclusions that the triad of cleft lip, palate, and lip pits was due to a single dominant gene with variable expressivity.

In their study of a five generation pedigree, Test and Fall[59] found an association of congenital lip pits with cleft lip and palate. The mode of inheritance of the pits seemed to be that of an autosomal dominant gene with incomplete penetrance.

Gorlin and Shapiro[126] reported that approximately 65 percent of the congenital lip pits observed were found in women; however, they felt that it was not possible to claim a genetic hypothesis from this observation. The authors attributed the high female percentage to a greater tendency in women to seek cosmetic relief.

In reviewing the literature it was noted that approximately 70 percent of the patients with mandibular lip pits have associated cleft lip and/or cleft palate. Furthermore, some affected families, because of the variable expressivity of the gene, exhibit only the lip pits, whereas, in other families some members exhibit only clefts and others have pits or a combination of pits and clefts.

Gorlin and Pindborg[127] proposed that a definite relationship exists between this triad and the popliteal pterygium syndrome. They maintained that a drawback to this theory is that the "lip pit" syndrome appears to be transmitted as an autosomal dominant trait, whereas the popliteal pterygium syndrome seems to be autosomal recessive.

Hall[128] reported a case of congenital lip pits associated with a cleft of the soft palate. It was not possible to obtain an accurate history of a similar condition in other members of the family; however, the paternal great-grandfather was reported to have had a cleft palate.

Commissural lip pits are believed to be a condition closely related to congenital lip pits. These pits occur at the lip commissures, lateral to the typical lip pits. Everett and Wescott[129] found that this condition seems to have an hereditary basis with an autosomal dominant mode of inheritance. This entity has also been seen with other congenital defects. There appears to be little published on this condition.

In looking for possible genetic carriers of cleft lip and palate, Fukuhara and Saito,[120] reported a number of possible "microforms" in relatives of

affected offspring. Using frontal, laminographic x-ray techniques, in addition to studying soft tissue configurations, the following characteristics were described: palatal bone defects, deviated nasal septum, rotation and crowding of the maxillary anterior teeth, congenital absence of the lateral and central incisors, and a raphé in the upper lip.

The relationship of ocular hypertelorism to cleft lip and palate has been discussed in the literature. Ocular hypertelorism is a congenital anomaly characterized by an excessive distance between the eyes. It was first described by Greig[130] in 1924.

Several investigators[131-133] consider hypertelorism merely a symptom or a descriptive term without etiologic implication. It was also thought to be a condition resulting from any type of craniofacial dysostosis.

In contrast, Gaard[134] claimed that this excessive spacing of the bony orbits was a specific etiologic entity and not a result of other craniofacial deformities.

Greig,[130] Kersley,[135] Posner and Piatt,[136] and Vorisek[137] noted that hypertelorism was a result of underdevelopment of the greater wings and relative

overgrowth of the lesser wings of the sphenoid bone. One investigator[138] attributed this anomaly to the hypertrophy of the body and greater wings of the sphenoid.

Muir,[139] in 1925, and Rawson and Avila,[140] in 1930 suggested that this condition was due to the persistence of the facial clefts.

Gorlin and Pindborg[127] proposed that developmental retardation of the craniofacial structures is an etiologic factor that must be considered. This assumption was based on the frequently associated finding of cleft lip and palate.

The oral manifestations most commonly seen with hypertelorism are a high arched palate, cleft lip and palate, and a few cases of bifid uvula.

Isola[141] believed that the reason for such a high incidence of palatal anomalies associated with hypertelorism could be attributed to the premature closure of the sphenotemporal suture, which interfered with the development of the greater wing and allowed over-development of the lesser wing of the sphenoid. This would lead to the palatal abnormality, since the under-development of this greater wing would result in a drawing in in all directions and consequently the

approximation of the pterygoid plates. This in turn would buckle the palate, causing it to have the extremely high narrow appearance, although it would not necessarily result in the palate being cleft.

Aitchinson[142] reported that two patients with marked hypertelorism also had missing maxillary permanent lateral incisors. Upon radiographic examination a cleft of the sphenoid and frontal bones was discovered.

Drummond[143] presented a case of hypertelorism in which four bicuspids were missing and the upper central incisors were mere stumps. The palate was extremely high and narrow.

In both of these papers no comments were made as to the relationship between facial clefts and hypertelorism.

Since hypertelorism by itself is rare (1/100,000 live births), only a few of these cases demonstrate a familial disposition for the anomaly.

Abernethy[144] discussed nine cases in which the anomaly appeared on the maternal side of the family. The proband upon clinical examination displayed a narrow and highly arched palate.

A case of hypertelorism associated with a high and narrow palate displayed a familial tendency in Allen's[145] study. Attention was directed to the parents and in both it was noted that the eyes were rather widely separated. No mention was made as to the parents' oral condition.

Brown and Harper[133] commented on two families which displayed hypertelorism. In discussing hypertelorism they noted not only the type of skull deformity with which hypertelorism may be associated but also the variety of abnormalities in the bones and soft tissues which frequently accompany it. Further comment was made concerning the mouth in that it frequently showed some abnormality. The palate was often highly arched and narrow and the gingiva hypertrophic. It was also stated that an abnormality of the mandible was uncommon.

Bojlem and Brems[146] studied 56 cases of hypertelorism reported in the literature and found that 14 were not true ocular hypertelorism. They ruled out cases in which the eyes were far apart secondarily to other disorders such as frontal meningocele and encephalocele. They also traced a family with hypertelorism through five generations and found 11 cases

among 24 members of the same family, the defect being transmitted as an autosomal dominant trait.

Another possible incomplete manifestation of cleft palate is that of bifid uvula.

Berans,[147] in 1893, noted that the prevalence of this anomaly was 1.82 percent This was based on a sample of 3,000 individuals.

McIntosh,[148] in 1954, examined 6,053 children and infants and found only 11 bifid uvula in his sample.

Meskin, Gorlin and Isaacson,[149] in 1964, counted 140 bifid clefts of the uvula in a sample of 9,701 individuals. The completeness of these clefts varied from a slight notch to a complete bifurcation of the cleft. In considering bifud uvula as a minor manifestation of the more severely involved cleft palate, the authors did not find a 2:1 female to male sex ration as has been frequently reported in cleft palate cases. The authors contend that the explanation for this is that as the palatal cleft becomes less severe, the sex affinity for the female also decreases. However, no conclusive evidence was submitted to substantiate this hypothesis.

VI. Risk Figures for Counseling

Various risk figures for the possible recurrence of cleft lip and cleft palate in a specific family were calculated by Schroder,[82-84] Fogh-Andersen,[29] Fraser,[24] Curtis and Walker,[71] and Curtis, Fraser and Warburton.[150] Since congenital clefts did not always show a familial tendency and did not conform to any simple Mendelian pattern of inheritance, empirical estimates of average probability were derived from the observed frequency of affected persons in each group of relatives. These percentages can be readily seen in Table V.

These risk figures provide estimates for counseling parents of affected individuals as well as the affected individuals themselves. However, these figures are not without limitations.

Even though various different categories were used, the risk figures of Fogh-Andersen, Curtis and Walker, and Curtis and associates were very similar. Schroder's calculations are not comparable since he did not separate cleft lip with or without cleft palate and isolated cleft palate.

STATEMENT OF THE PROBLEM

The first consideration in the writing of this thesis was to acquaint the reader with the complexities involved in an etiologic study of cleft lip and cleft palate. It is hoped that the review of the literature succeeded in demonstrating that the etiology of cleft lip and cleft palate is not a clearly defined one, but involves a complicated interaction between multiple genetic predispositions and various ill-defined environmental factors.

The second objective of this study was to provide additional information in identifying the so-called "microforms" or incomplete manifestations of cleft lip and cleft palate. Furthermore, an attempt has been made to determine how these "microforms" might alter the apparent mode of inheritance in families displaying a familial disposition for cleft lip and cleft palate.

EXPERIMENTAL PROCEDURE

Sample selection

In selecting families displaying a possible familial pattern for cleft lip and cleft palate, a family history was obtained from the parents of 206 children affected with cleft lip and/or cleft palate who were admitted as patients to the James Whitcomb Riley Children's Hospital Dental Clinic.

The diagnosis was confirmed by a thorough examination of the child's medical and dental histories as well as the questioning of both parents. In every case the line of questioning was directed towards any knowledge of individuals with cleft lip and/or cleft palate on either side of the family. If others in the family were affected, the relationship of the individual to the affected child (proband) was noted.

The presence of at least one affected parent, sibling, or first cousin of the proband was used as the criteria for the inclusion of a family in this study. This criterion was used in order to minimize the possibility of multiple sporadic (non-genetic) cases occurring in a pedigree.

Pedigree material

Pedigrees of the families selected for study were assembled at the Department of Medical Genetics in the

Indiana University Medical Center. A majority of the pedigrees were constructed by interviewing the parents when they brought their child to the Riley Dental Clinic. When this was not possible special appointments for interviews were made through the Medical Genetics Department or the investigator visited the home of these families. All reported clefts among the relatives, when possible, were verified by individual examination, hospital records, or photographs.

Once the pedigree was constructed the author and a member (D.B.) of the Dental Genetics Department analyzed the pedigree. From this analysis specific individuals were selected from the individual families to be examined clinically and radiographically. This selection was made for the individuals in the pedigree who were not cleft themselves, but who were members on the side of the family which had a history for clefting. This group included the proband's parents, siblings, grandparents, uncles, aunts, and first cousins.

Clinical examination for oral and facial discrepancies

Once the pedigree analysis and selection of the individuals to be examined was completed, the following tissue discrepancies of the oral and paraoral

structures, if present, were noted:

1. Bifid uvula
2. Raphe of the upper lip
3. Notching of the alveolus
4. Mandibular lip pits
5. Commissural fissures
6. Accentuated asymmetrical nasal shape (nares in particular)
7. Malformed Maxillary central and lateral incisors
8. Congenitally missing maxillary central and laterally incisors
9. Excessive crowding of teeth in the anterior segment of the maxillary arch

Selection of these tissue discrepancies was based upon the embryological development of the lip and palate. Furthermore, it was also decided that any surrounding structures which would be affected by the clefting should be included. These structures therefore would have to include the maxillary incisors.

In every instance a good light and tongue depressor was used in the direct intra-oral examination. When the uvula was examined for clefting, a tongue blade was used to separate the cleft parts, if any

possibility of a uvular cleft was noted.

The area observed in the search for a raphe in the upper lip or a notching of the alveolus was founded on the theory of mesodermal penetration during the development of the primary palate. Therefore, the tissue examined was in the area labial to the incisive suture of the premaxilla and palate. Since the maxillary central and lateral incisors and the cuspids are in this area, any anatomical discrepancies or gross malalignment of these teeth within the arch was noted.

Examination for mandibular lip pits included the area encompassed by the vermillion border of the lip to the junction of the intra-oral mucosa. It was also felt that the commissural lip pits were closely related to the mandibular lip pits in that they occur at the site of a potential horizontal facial cleft. A thorough digital examination of the junction of the upper and lower lip was therefore included.

In examining for asymmetry of the nares, the patient's head was tilted back to a point approximately parallel to the floor. The nose was then examined for any deviation to the right or left, gross discrepancy in the size of the nostrils, and the position of the

nasal septum. The patient was also questioned as to the possibility of any previous history of trauma or surgery done to the nose. The premise in this case being that abnormal development in the hard structures of the primary palate, which was not clinically apparent may be intimately related to and indicated by such abnormal nasal findings.

These foregoing conditions were noted and recorded on 35 millimeter Kodachrome slides.

Clinical and Roentgenographic Examination for Hypertelorism

The examination of the patients for hypertelorism consisted of both soft tissue and skeletal measurements. The following measurements were used:

1. Canthal index*
2. Circumference-interorbital index**

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*Canthal index = $\frac{\text{inter canthus distance}}{\text{outer canthus distance}} \times 100$

** Circumference-interorbital index =

$$\frac{\text{inter canthus distance}}{\text{occipital-frontal circumference}} \times 100$$

3. Intercorneal distance

4. Skeletal interorbital distance

Since the diagnosis of hypertelorism is primarily defined through the canthal index and the circumference-interorbital index, the following measurements were necessary:

1. Intercanthal distance: measured by having the patient sit in an upright position allowing the eyes to be parallel to the floor. Using a 250 millimeter sliding caliper* and placing the pointed branch ends at the intercanthi of both eyes. The millimeter scale was held parallel with the patient's forehead.
2. Outercanthal distance: obtained in a similar manner as the intercanthal distance.
3. Occipital-frontal circumference: obtained by placing a millimeter tape measure* superior to the occipital region and bringing the tape directly over the superior borders of the orbits.

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*G.P.M. Anthropological instruments, Siber Hegner and Company Incorporated

The skeletal interorbital measurements were taken from a posterior-anterior cephalometric headplate. In order to standardize all of the headplates, the patients were placed in a Broadbent-Bolton cephalometer located in the Orthodontic Department at the Indiana University School of Dentistry. The headplates were then placed on a radiographic viewbox and acetate paper was placed over the headplates. Tracings of the medial walls of the orbit were recorded. If the orbital outline was extremely thick, the line was drawn through the middle of the outline. Lines tangent to the arcs of the orbit and parallel to a baseline were then drawn. A bow divider was then placed on each tangent. This distance was then measured by a millimeter ruler.

A control group of 70 Caucasian individuals ranging from four to 22 years of age was selected at random from patients, students, and employees at the Indiana School of Dentistry. The patients themselves were taken from the pedodontic, orthodontic, and dental hygiene clinics. Identical optical measurements were taken and then compared with the results compiled from the individuals in families afflicted with cleft lip and palate. The results from these

two groups were then compared to the normal values for the canthal and circumference-interorbital indices proposed by Günther[151] and the orbital findings of Silverman[152] and Jöhr.[153]

The rationale behind the use of these optical measurements was based on the assumption that abnormal growth of the sphenoid bone, of which the anterior surface of its greater wing comprises a large portion of the orbit. It has been demonstrated in animals that palatal closure may be prevented by lateral head growth which prevents contact of the palatal shelves. Orbit position then may well be a reflection of such lateral growth.[8,24-26]

History of pregnancy

A questionaire was compiled with the aid of the Department of Psychiatry in the Indiana University Medical Center (Figure 3). These questionaires were sent to physicians who examined and treated the probands' mothers during pregnancy.

Since the parents of these affected children conceivably are carriers for a gene or genes involving cleft lip and palate formation, an attempt was made to eliminate a possible environmental cause.

RESULTS

Sample selection

Family histories in which there were 206 children affected with cleft lip and/or cleft palate were reduced to 22 families in which there was more than one occurrence of cleft lip and/or cleft palate. The presence of at least one affected parent, sibling, or first cousin of the affected proband was noted in 18 of these families; these were selected for study because of the close genetic relationship of the affected individuals. In one family the affected sibling of the proband was an identical twin. Both individuals were treated as one occurrence and were eliminated from this study. Three of the families with a history of multiple occurrences of cleft lip or cleft palate changed residence after the initial contact and could not be located for follow up study. The parents and siblings of three additional families were separated due to the divorce of the parents and co-operation for further study could not be obtained. Therefore, a total of 11 families remained for the present study.

Frequency of facial and oral discrepancies in relatives of probands with cleft lip with or without cleft palate and isolated cleft palate

The frequency of bifid uvula in the relatives of probands with cleft lip and/or cleft palate in the

present study was compared to the frequency of bifid uvula in the general population as demonstrated by Meskin and his associates (1.47 percent) and confirmed in the smaller studies of Berans[147] (1.82 percent) and Baker[154] (1.7 percent). There was a highly significant difference in the frequency of bifid uvula between Meskin's results and this study (X^2 = 31.1; d.f. = 1; $p < .001$). Therefore, the sample of 11 families included in the present study was not a random sample of the general population, with regard to the prevalence of bifid uvula. An equal distribution of the trait among males and females (five males-five females) was noted. Of the 11 families studied, six (54.5 percent) contained at least one individual with bifid uvula (Table VI). Two families had more than one individual with bifid uvula (Figures 6 and 16). One family exhibited one sibling with isolated cleft palate and one sibling with a bifid uvula (Figure 9).

Seven individuals, other than the proband within two of the 11 families in this study, demonstrated mandibular lip pits (Figure 23) making a total of nine affected individuals (Table VI). Since the occurrence of mandibular lip pits in the general population is extremely rare and has never been reported, statistical

comparisons of these data could not be made. Six of the individuals affected with mandibular lip pits belong to Family I. The seventh individual, since she represents an isolated occurrence in the pedigree, is most likely sporadic (Figure 14).

Commissural lip pits (Figure 22) occurred in 19 of 138 (13.9 percent) individuals. When compared to an observed frequency in a select population (Baker's findings in a young adult group at Chanute Air Force Base[154]) no significant difference was found (X2=.819; d.f.=1; NS). However, seven of the 11 families (63.7 percent) included in the present study demonstrated these lip pits. Males were affected approximately twice as frequently as females (13 to 6).

Three individuals had congenitally missing or malformed maxillary lateral incisors. Two of the three individuals had siblings with cleft lip and cleft palate (Figures 10 and 15) while the remaining affected individual was the parent of two siblings affected with cleft lip and cleft palate (Figure 6). The frequency of missing lateral incisors in the general population has been estimated at 1.05 percent.[155] The difference between the frequency observed in this study and in the general population was found to be significant ($X^2 = 4.0$; d.f.=1; $p < .05$).

Three of the 111 individuals in the present study had malformed maxillary central and lateral incisors (Table VI). None of these three affected individuals were from the same family and all of the affected lateral incisors were of the peg-shaped variety. The frequency of maxillary pegged lateral incisors observed in this study (2.7 percent) was not significantly different from that of 1.78 percent observed in the general population[156] (X^2 = .45; d.f.= 1; NS). Since all of the affected individuals with congenitally missing and malformed maxillary lateral incisors belonged to different families and because of the small number found in this group, the value of this portion of the study remains questionable.

Two of the 11 families included in this study presented a total of two individuals with a raphé of the upper lip, one of whom also had asymmetrical shape of the nares. Both of these affected individuals were parents of at least one child wich cleft lip and cleft palate (Figures 10 and 12). These manifestations would indicate the importance of their observation in cleft lip and cleft palate families. One other individual had an extreme discrepancy in symmetry of the nares but no apparent oral deformity. He was

both the father and uncle of children affected with cleft lip and cleft palate (Figure 16). Finding these three subjects with such visible defects supports the assumption that individuals carrying the gene for cleft lip and palate may be present. This hypothesis is further strengthened by the fact that all three of these individuals have had at least one child with cleft lip and cleft palate.

Notching of the maxillary alveolar process, as described by Fukahara and Saito[120] -- sometimes seen in incomplete clefts of the lip -- was not observed in any of the 138 subjects examined. The two individuals with a raphé of the upper lip had no apparent alveolar involvement.

Owing to the great frequency and variation of malocclusion in the general population and to the limited number of subjects affected with extreme crowding of the maxillary anterior teeth in this study, the relationship of malocclusion to cleft lip and cleft palate was given no consideration in the final analysis of data from this study.

Examination of single facial and oral discrepancies for specific hereditary patterns

Since commissural lip pits, mandibular lip pits, and bifid uvula displayed a high prevalence among the

individuals in the families of this study, an examination for a specific mode of inheritance was attempted for each entity.

Family I (Figure 6), in which six of the seven observed cases of mandibular lip pits occurred, demonstrated an autosomal dominant mode of inheritance for this condition. Using the method of complete ascertainment*, a four-to-one ratio of affected-to-normal individuals was noted in the second generation. In the third generation, assuming that the affected in the second generation are heterozygous for the "lip pit gene", a two-to-three ratio was observed, which seemed to support an autosomal dominant hypothesis. Furthermore, by including cleft lip and cleft palate in the pedigree, the occurrence of the triad of mandibular lip pits, cleft lip, and cleft palate seemed to be due to a single dominant gene with variable expressivity. This confirms Van der Woude's[47] observations.

The distribution of the condition of commissural lip pits was found to be approximately two-to-one in favor of males. Because of the very small sample, a method of complete ascertainment* was employed to

*Stern, Curtis: Principles of Human Genetics. 2nd ed. San Francisco, W. H. Freeman Co., 1960, p. 133.

confirm the given sex ratio. This procedure altered the male-female ratio to one-to-one. Therefore, any hypothesis of sex-linkage was weakened. Commissural lip pits in these families seemed to be transmitted by an autosomal dominant gene.

No definite hereditary pattern for the condition of bifid uvula alone was found. Four of the 10 affected individuals were found in Family XI (Figure 16) and in this family the trait appeared to be transmitted by a dominant gene. The other occurrences were spread out in five other pedigrees. The observed one-to-one sex ratio of bifid uvula confirmed the findings of Meskin and his associates.[149]

Examination of multiple facial and oral discrepancies for specific hereditary patterns

As described earlier, no obvious hereditary patterns were apparent for bifid uvula alone or commissural lip pits alone although the former seemed to have a dominant mode of inheritance in Family XI and the latter appeared as a dominant trait in Families I, III, IV. Since the isolated conditions of bifid uvula and commissural lip pits did not make a discernable pattern, an attempt was made to make various combinations of these two traits with cleft lip and/or cleft palate and analyze the

resultant segregation ratios (Families I, III-VIII, XI). The combinations considered were cleft lip and cleft palate with bifid uvula and commissural lip pits; cleft lip and cleft palate with bifid uvula; bifid uvula and isolated cleft palate; and commissural lip pits with cleft lip and cleft palate. These combinations are shown in Table VII.

When the traits cleft lip, cleft palate, bifid uvula, and commissural lip pits were considered as varying manifestations of the same entity, clefting, a segregation analysis produced a 31:41 ratio among the affected and non-affected individuals in the sibling population. A similar ratio was obtained when commissural lip pits and bifid uvula were combined. The attained ratio suggested autosomal dominance with approximately 75 percent penetrance. When this mode of inheritance was applied to the individual pedigrees, autosomal dominance with reduced penetrance was apparent in each instance (Figures 6, 8, 11-13, 16).

When the bifid uvula and cleft lip with or without cleft palate were considered together (Figures 6, 9-12, 16) a two-to-three ratio of affected to non-affected subjects in the sibling population was observed.

Furthermore, when bifid uvula and isolated cleft palate were combined a one-to-two ratio of affected to non-affected subjects in the sibling population was observed (Figures 6, 9-14, 16). The latter ratio suggested autosomal dominance with 50 percent penetrance, but the numbers of affected individuals were too small to draw conclusions.

Although the various combinations of oral anomalies used in this study were interesting to investigate, their inclusion in the analysis of incomplete manifestations of cleft lip and cleft palate did not make any particular mode of inheritance seem apparent. In fact, these results clearly demonstrated that when bifid uvula and commissural lip pits were considered in various combinations with cleft lip and/or cleft palate no obvious change in the manner of inheritance of the clefts were observed. Commissural lip pits and bifid uvula, actually appeared to be presenting themselves independently of the cleft lip and cleft palate condition.

History of pregnancy

The medical histories of probands' mothers during pregnancy provided a minimal amount of pertinent information. However, two mothers had difficulty dur-

ing pregnancy with the proband (Families VII, VIII). The proband's mother in Family VII had an ovary removed during the second trimester. In Family VIII, the proband's mother threatened abortion during the second month of pregnancy and was hospitalized for two days. Interestingly, both husbands of these women had a cleft lip and a cleft palate.

The mother of the proband in Family III was placed on thyroid medication during two of her pregnancies, each of which resulted in affected children, one child with cleft lip and cleft palate and one with isolated cleft lip.

Results of clinical and roentgenographic examination for hypertelorism

In considering the biostatistical analysis to be used in determining any significant differences in the ocular and orbital measurements of the control group and the unaffected individuals in families with a history of cleft lip and/or cleft palate, a number of variables were considered. These included age and sex in both groups and the sex of the proband, relationship to the proband, and maternal or paternal history of cleft lip and/or cleft palate in the relatives of probands with a family history of clefting group. The observed oral and facial discrepancies

alone with the ocular and orbital measurements were coded and placed on a Coding Form-Master Card. This was done in order to facilitate the placement of these data on computer cards.

When the frequency distribution of each variable was being considered, it became apparent that there would be an insufficient number of subjects available for each group and that one or more of these variables would have to be excluded. Therefore, only age, sex, and the relationship to the proband (coefficient of relationship) were used. Furthermore, in a preliminary analysis of the ocular and orbital measurements, it was noted that many of these measurements were highly correlated (Tables IX, X) and that a meaningful analysis between the relatives of the proband in families with a history of clefting and control groups could not be obtained if each of these measurements were treated as a separate variable. Since many of the ocular and orbital measurements vary with age and possibly the sex of the individuals,[152,153,157] it was necessary to include the age and sex variables when comparing the two groups.

Therefore, multivariate procedures were considered to be the most appropriate statistical method in

analyzing these data. Specifically, a step-wise multiple regression analysis[158] was used with group membership; the control group and the relatives of the proband in families with a history of cleft lip and cleft palate group, comprised the dependent variable. The seven ocular and orbital measurements were used as the independent variables (Tables XI, XII, XIII). In order to correct for any differences attributable to the effects of age and sex on these measurement (independent variables) within the two groups, age, sex, and age-squared were used as control variables. The rationale for the use of age-squared as a control variable was based on the fact that a number of these measurements do not change linearly with age but rather increase at a decreasing velocity resulting in a curvilinear curve which reaches a plateau at a specific age.[152,153] Therefore, the BIMED-03R step-wise regression program developed at the Computing Center, UCLA, was used to analyze these data on the CDC 3600 Computer. The degree of difference between the ocular and orbital measurements in the two groups was accepted as significant only at the five percent level of confidence or less.

In order to qualify for this analysis all seven

ocular and orbital measurements must have been taken on each individual. One hundred and sixty-six individuals contributed complete information. Of these 166, 66 were from the control group.

When ocular and orbital measurements of the two groups were analyzed, a significantly smaller canthal index was found in the relatives of a proband with a family history of clefting group ($p < .05$). The circumference-interorbital index was significantly larger in the relatives of a proband with a family history of clefting group ($p < .001$); and the skeletal interorbital distance was significantly smaller in the relatives of a proband with a family history of clefting group ($p < .025$) (Table XIV). The control variable, age, was shown to have significantly contributed to the differences obtained for ocular and orbital measurements within the individuals of both the relatives of a proband with a family history of clefting and control groups ($p < .01$). This was anticipated since growth increases with age.

To determine more specifically where the significant differences occurred in the relatives of a proband with a family history of clefting group a stepwise regression analysis was completed using the co-

efficient of relationship as the dependent variable and age, age squared, sex, and the ocular and orbital measurements as the independent variables. The rationale used in attempting this test was to demonstrate if the significant differences found in the ocular and orbital measurements between the two groups (canthal-index, circumference interorbital, and skeletal interorbital) could be attributed to the relatives closest to the proband. Therefore, the closer the relative to the proband, the greater the difference one might expect to find within the relatives of the proband with a family history of clefting group. However, this difference could not be demonstrated; the three variables which were significantly different between the control and the relatives of a proband with a family history of clefting groups were non-significant when the relatives of a proband with a family history of clefting group was analyzed using the degree of relationship as the dependent variable (Table XV).

FIGURES AND TABLES

Figure 1. Orban[2] describes the six stages in the development of the primary palate.

A. Human embryo nine millimeters in length.

B. Epithelial wall formed by the union of the median nasal process with the maxillary process.

C. Blind olfactory sac formed by closed nasal pit. The primary union of the medial nasal, maxillary, and lateral processes has occurred. The epithelial wall has lengthened. The arrow points to the area in which the epithelial wall separates the olfactory sac from the oral cavity.

D. The mesoderm has broken through the superior part of the epithelial, thus strengthening the primary epithelial fusion of median nasal process to the maxillary and lateral processes. The inferior part of the epithelial wall has thinned out (arrow).

E. The destruction of the superior part of the epithelial wall by proliferating mesoderm has advanced. The inferior part of the epithelial wall is thinned out to form the nasobuccal membrane.

F. The nasobuccal membrane has ruptured. Nasal cavity communicates with oral cavity through primary choana (arrow). The superior part of the epithelial wall is entirely replaced by proliferating mesoderm forming the primary palate between nasal and oral cavities.

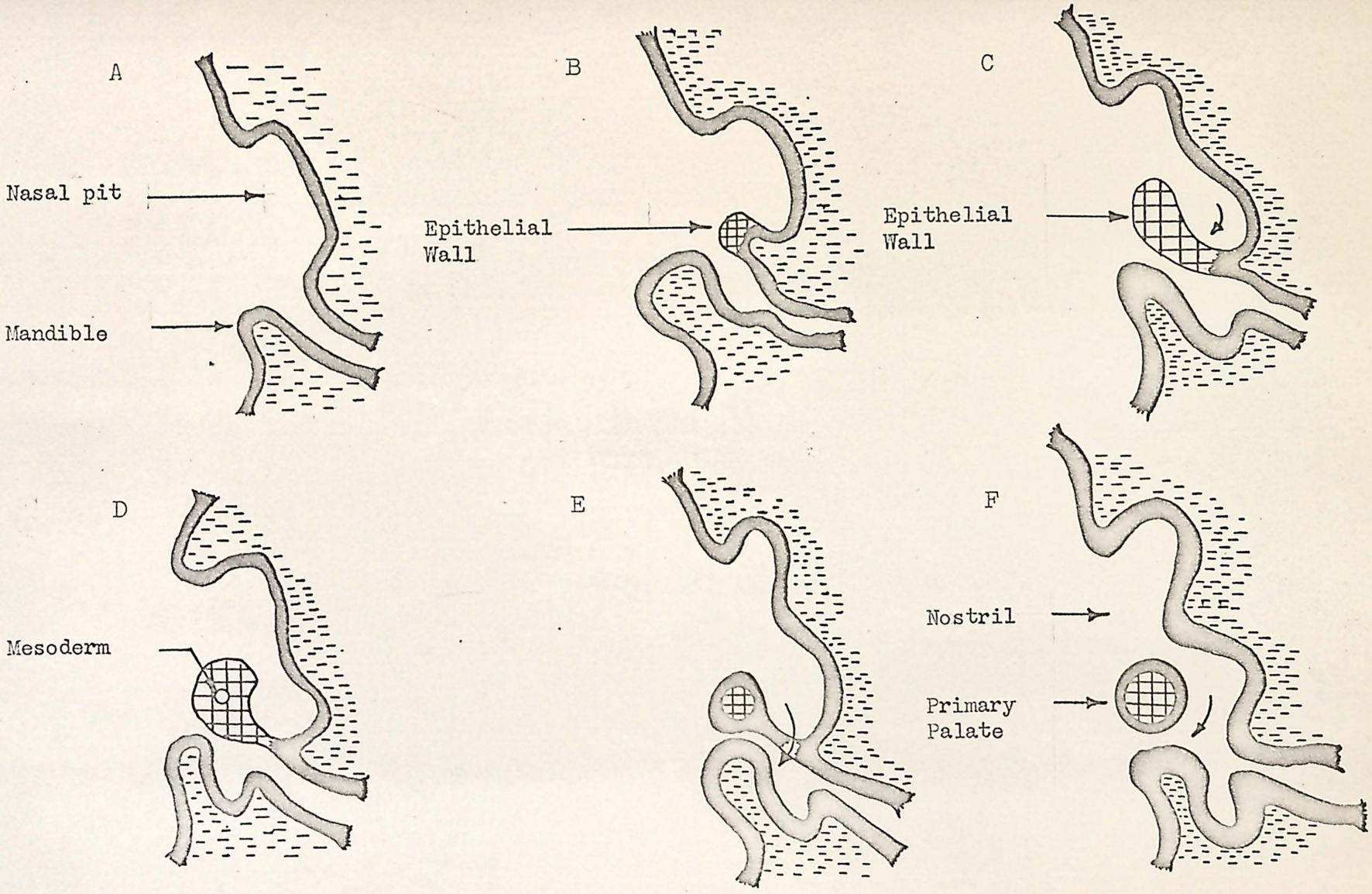

A
Nasal pit
Mandible
B
Epithelial
Wall
C
Epithelial
Wall
D
Mesoderm
E
F
Nostril
Primary
Palate

Figure 2. Timetable of development of the central face. Relative sequence and time of development of the disparate parts of the central face. (From Stark[11])

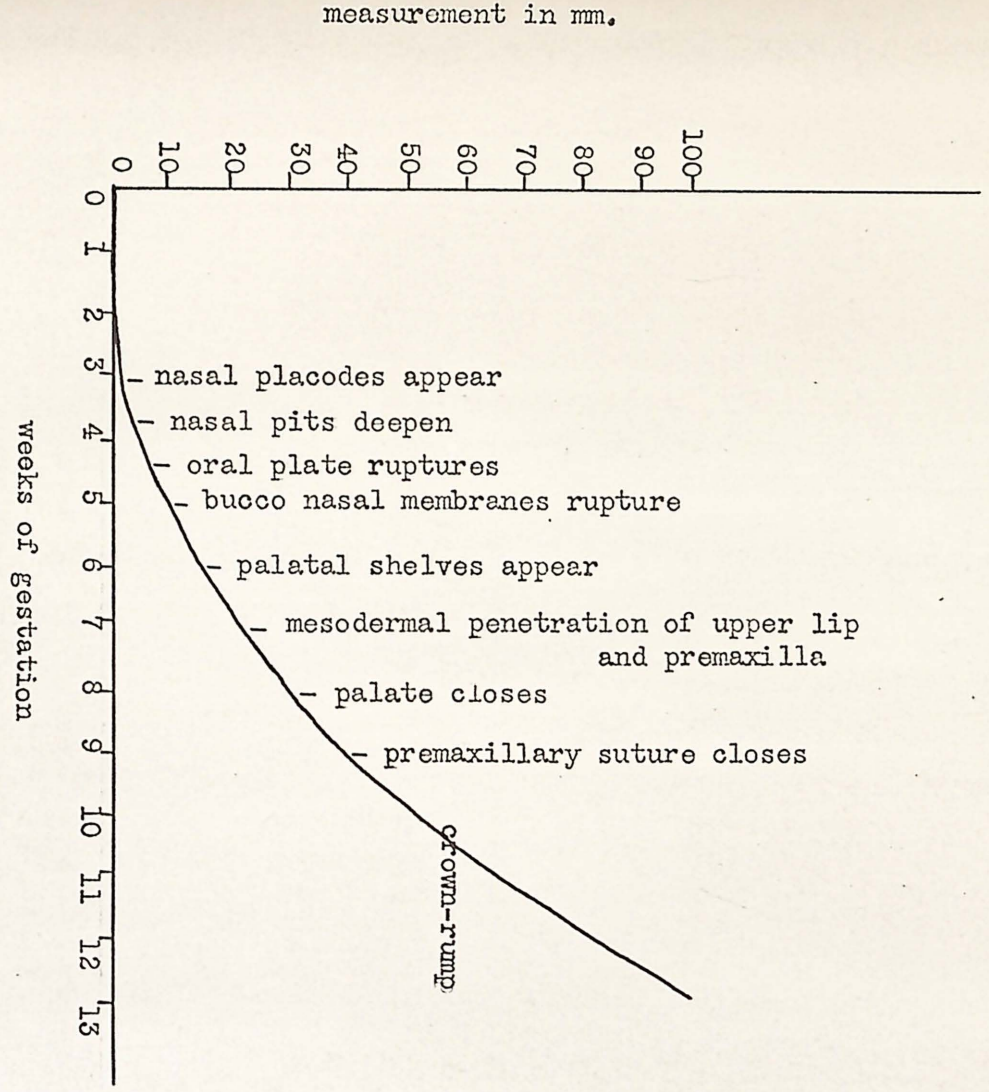

measurement in mm.
0
10
20
30
40
50
60
70
80
90
100
0
1
2
3
4
5
6
7
8
9
10
11
12
13
weeks of gestation
nasal placodes appear
nasal pits deepen
oral plate ruptures
bucco nasal membranes rupture
palatal shelves appear
mesodermal penetration of upper lip and premaxilla
palate closes
premaxillary suture closes
crown-rump

Figure 3. Questionaire sent to the physicians who examined and treated the probands' mothers during pregnancy.

Please circle answers which relate to this patient's pregnancy and fill in the short answers where indicated.

Patient:_____

Address_____
Street and Number City State

Child's Name:_____

Weight of mother at first appointment:_____

Birth Rank of Child: 1st, 2nd, 3rd, 4th, or _____

Birth Weight of Child:_____

I. What was the general health status of the patient during pregnancy:
Good Fair Poor

If Fair or Poor, give major pathological conditions (diabetes, anemias, etc.:

II. Did the patient have a history of miscarriage? Yes No

If Yes, what was the etiologic factor (if known):

III. Were there any complications during the pregnancy? Yes No
If Yes:
A. Threatened abortion? Yes No
B. Major surgery not related to pregnancy? Yes No
C. Patient have any severe falls or accidents? Yes No
IF YES, during what month?_____

IV. Did the patient have any severe emotional problems, such as excessive worry during the pregnancy? Yes No

V. Did the patient have a weight problem? Yes No

How was it controlled? (Drugs, etc.):

VI. Did the patient have any allergies which were manifested during the pregnancy? Yes No

Figure 4. Symbols used in constructing the pedigrees drawn from this study.

PEDIGREE SYMBOLS

Male

5 males

Female

3 females

Sex unknown

8 Sex unknown, e.g.: 8 siblings

Examined professionally; affected with trait

Not examined professionally; reported to have trait

Examined professionally; normal for trait

Not examined; reported normal for trait

Adopted

Marriage

Consanguineous marriage

Illegitimacy

No issue

Identical twins

FR Fraternal twins

Smaller symbols:

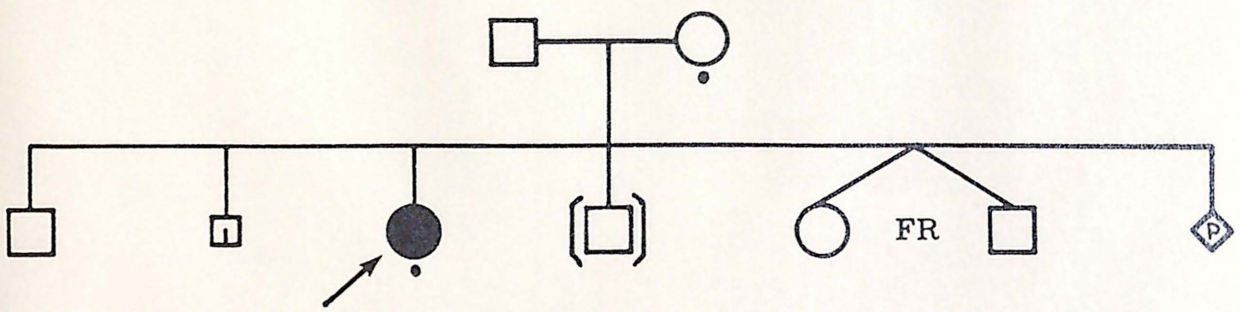
Lived less than one day

P Pregnancy

Stillbirth

Miscarriage

EXAMPLE OF SYMBOL USE
(Marriage and Sibship)



Indicate index case (probands) with arrow.

Figure 5. Symbols used to indicate specific anomalies found in families included in this study.

1.  CLEFT LIP

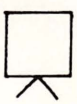
2.  CLEFT PALATE

3.  BIFID UVULA

4.  MANDIBULAR LIP PITS

5.  CONGENITALLY MISSING CENTRALS AND LATERALS

6.  MALFORMED CENTRALS AND LATERALS

7.  OR  COMMISSURAL LIP PITS

8.  ASYMMETRICAL NASAL SHAPE

9.  NOTCHING OF ALVEOLUS

10.  NOTCHING OF LIP

11.  EXCESSIVE CROWDING OF MAXILLARY ANTERIOR TEETH

12.  POSSIBLE HYPERTELORISM

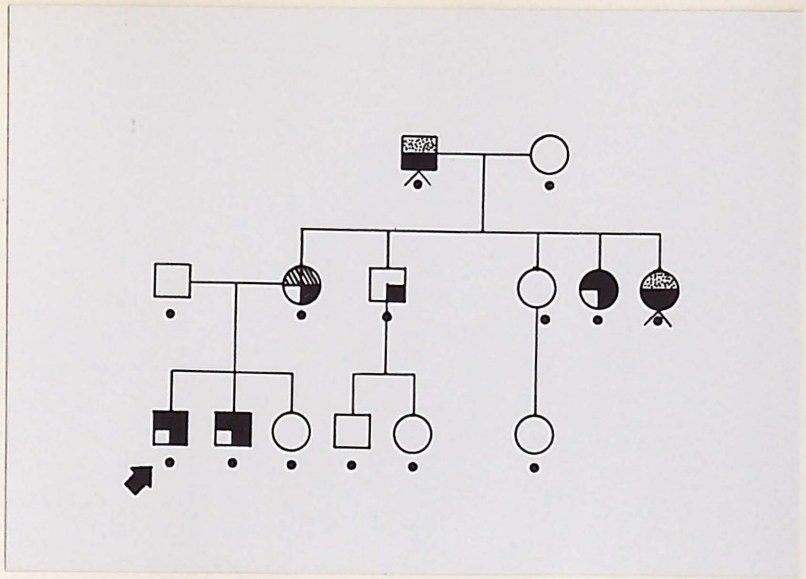
13.  CRANIAL DEFORMITY

14.  DEATH IN INFANCY

15.  DECEASED

Figure 6. Constructed pedigree of Family I.

Figure 7. Constructed pedigree of Family II.



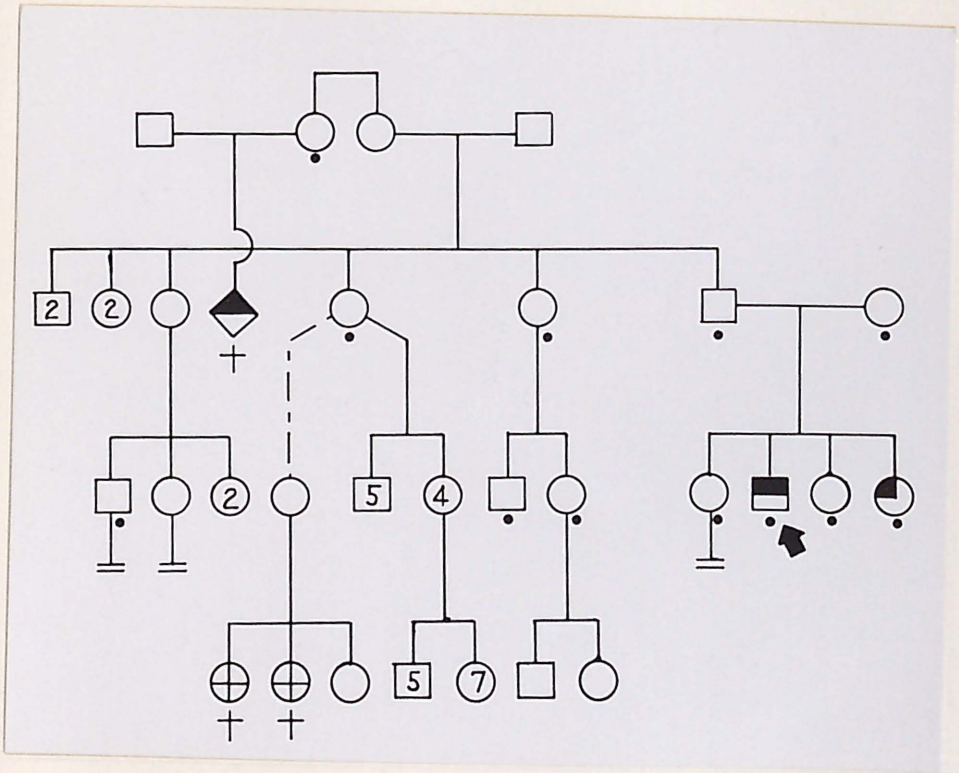
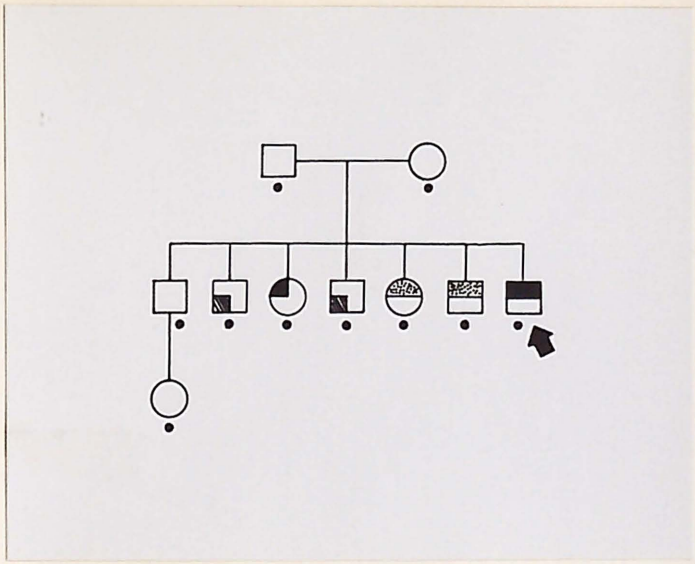

2
2
2
5
4
5
7

Figure 8. Constructed pedigree of Family III.

Figure 9. Constructed pedigree of family IV.



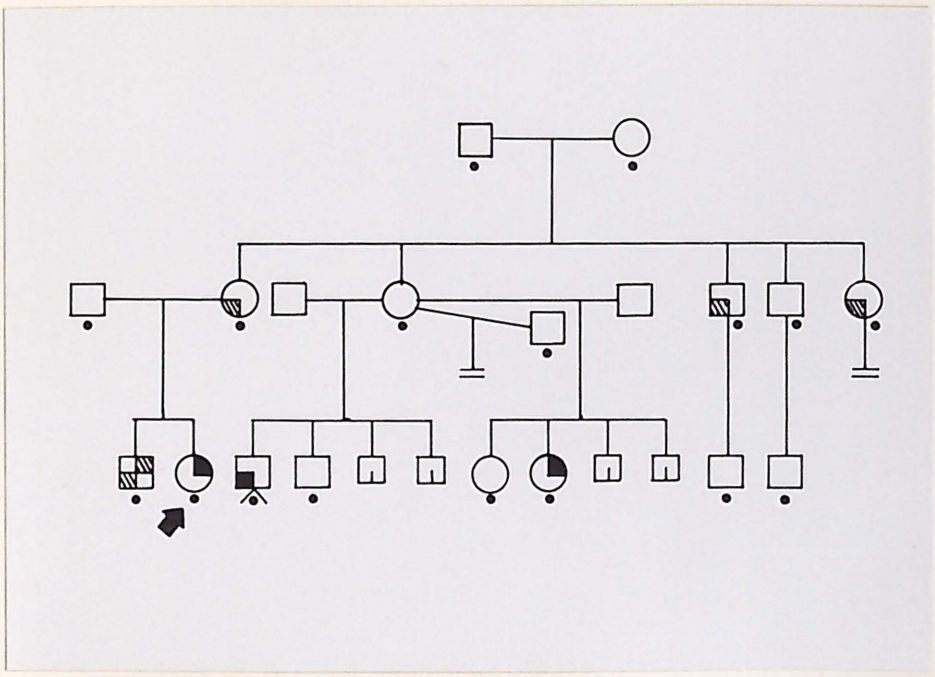
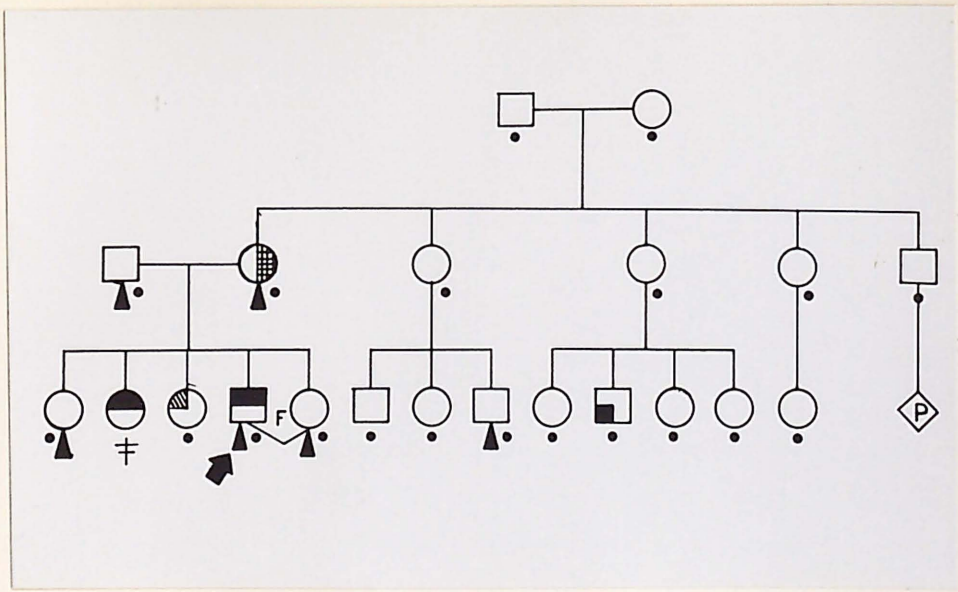


Figure 10. Constructed pedigree of Family V.

Figure 11. Constructed pedigree of Family VI.


F
P

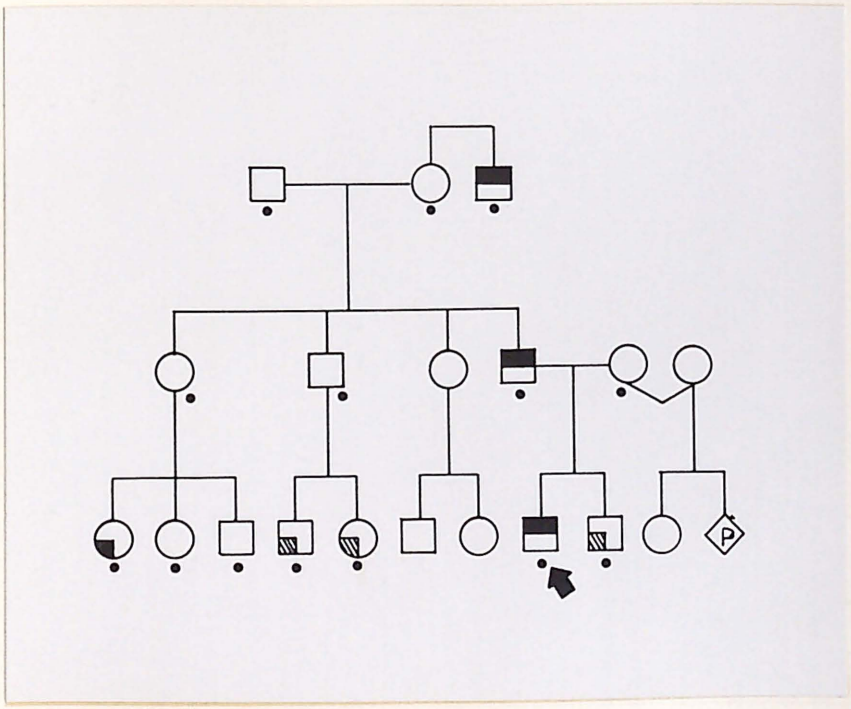
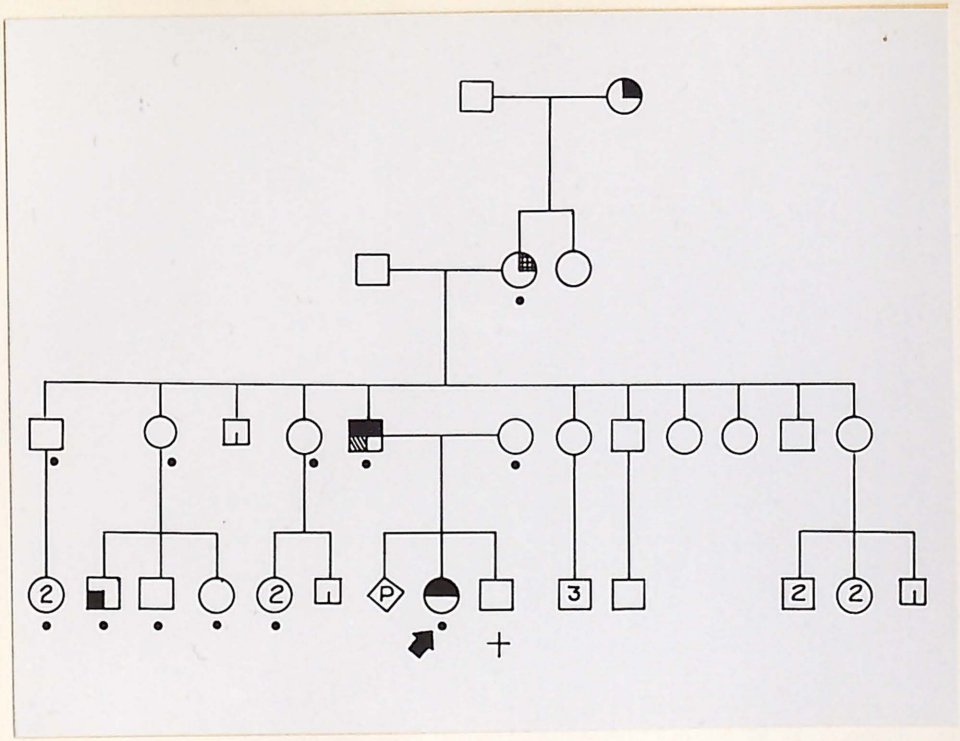

P

Figure 12. Constructed pedigree of Family VII.

Figure 13. Constructed pedigree of Family VIII.


2
2
P
3
2
2

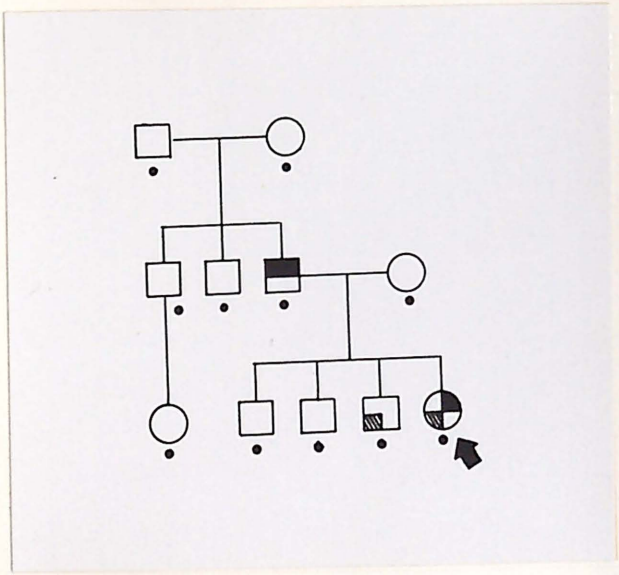
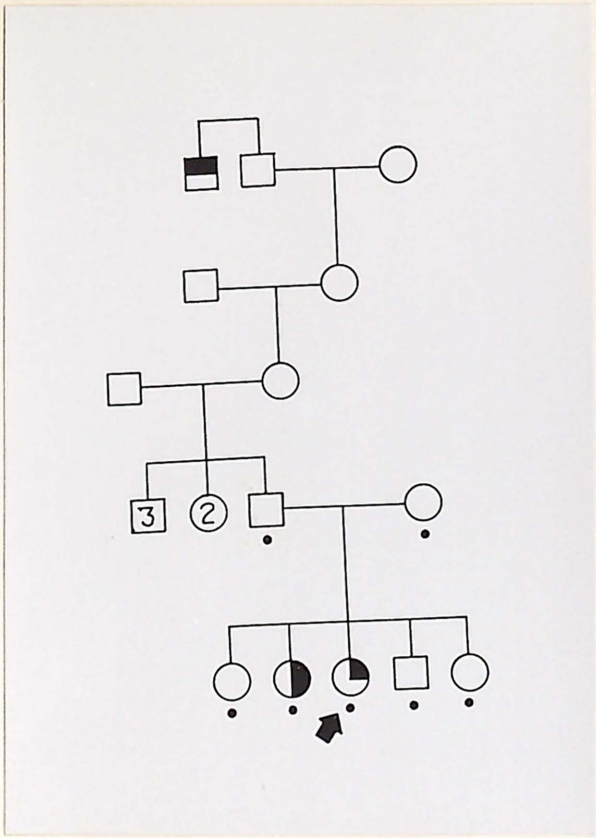


Figure 14. Constructed pedigree of Family IX.

Figure 15. Constructed pedigree of Family X.


3
2

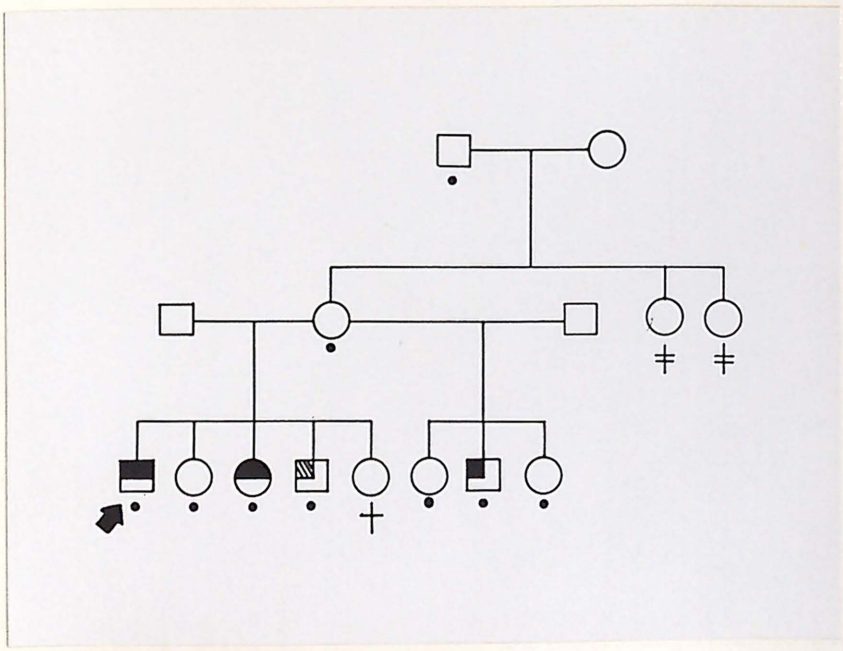


Figure 16. Constructed pedigree of Family XI.

Figure 17. A pre-school child exhibiting overt hypertelorism with a cleft lip and cleft palate.

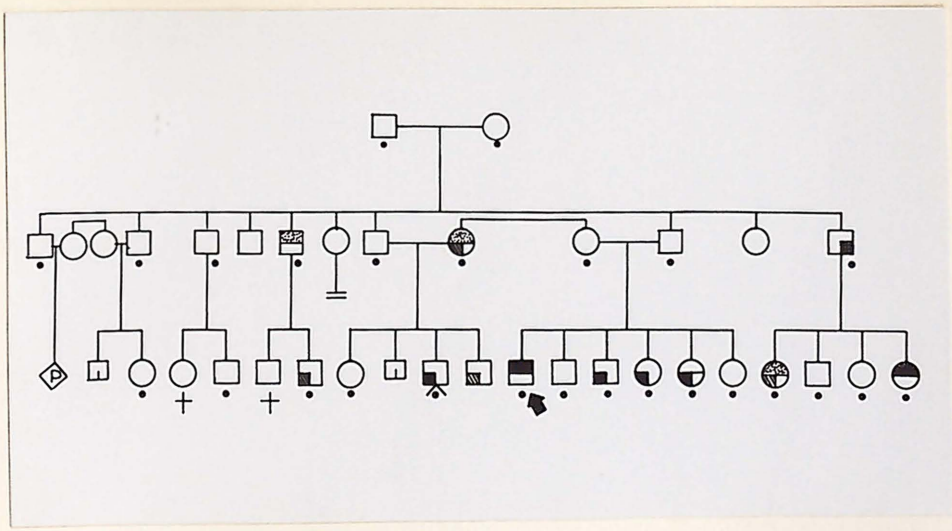


Figure 18. Asymmetry of the nose as exhibited by a parent who bore children with cleft lip and cleft palate.

Figure 19. Notching of the lip as exhibited by a parent who bore two children with cleft lip and cleft palate (arrow).

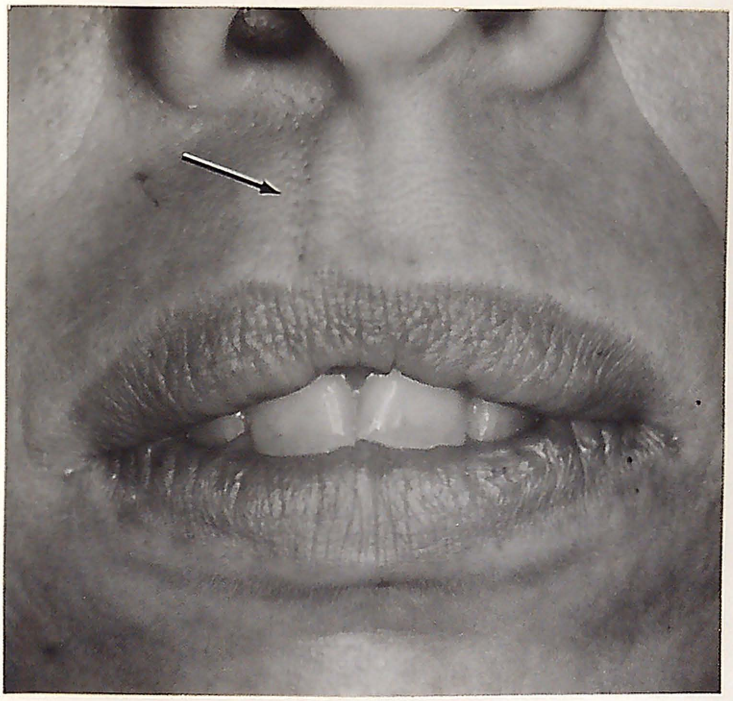
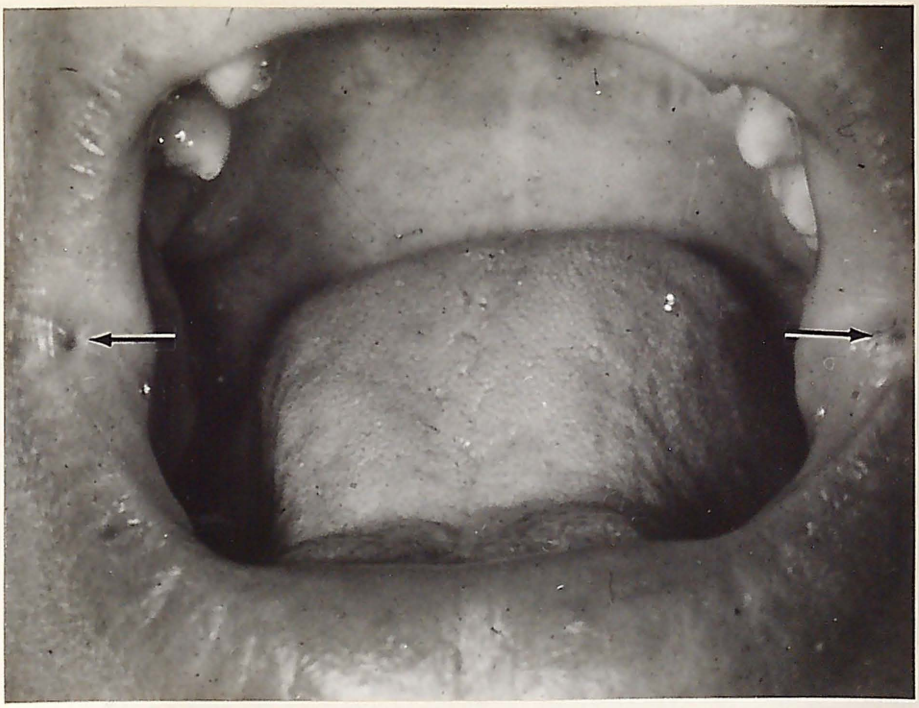


Figure 20. Congenitally missing and peg-shaped maxillary lateral incisors as exhibited by a parent who bore two children with cleft lip and cleft palate (arrows).

Figure 21. One degree of bifid uvula found in relatives of probands with clefting examined in this study.

Figure 22. Commissural lip pits as exhibited in a number of relatives of probands with clefting examined in this study (arrows).

Figure 23. Mandibular lip pits as demonstrated in Families I and IX.



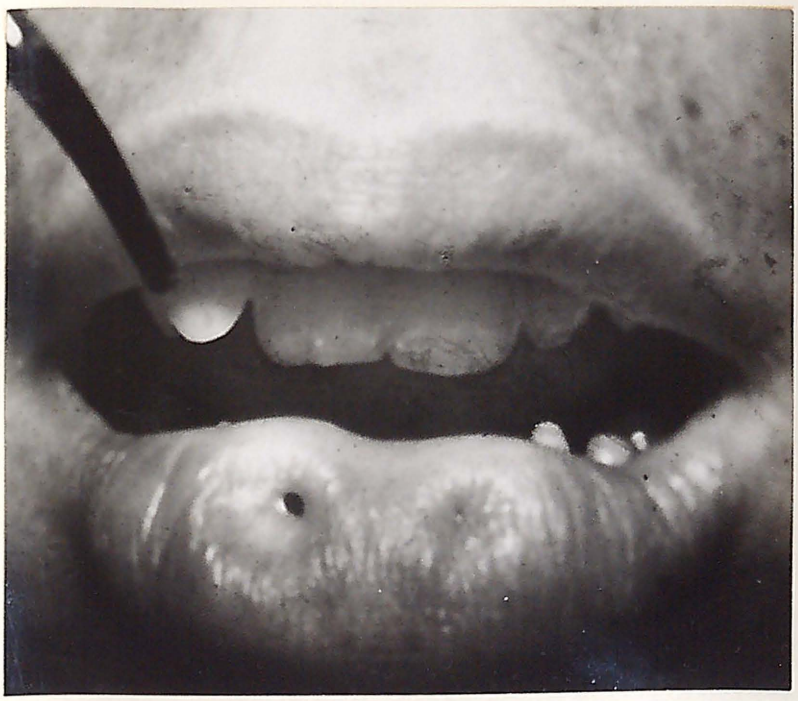


Table I. Time table of human development*

Age (Days)	Size (mm.)	General Body Form
1	.100	Zygote
25	3.000	Rupture of buccopharyngeal membrane
56	25.000	Facial clefts closed-eyelids formed
56	26.000	Palatal processes grow medially
63	35.000	Fusion of palate complete

Age is given as ovulation age, which is two weeks less than the age calculated from the first day of the last menstrual period. Size is given as from crown to rump length.

*From Millen,[18] proposed by Streeter, Arey, and Dittmer.

Table II. Reported incidence of cleft lip and cleft palate

Year	Author	Place	No. in Total Population	Incidence
1864	Frobelius	St. Petersburg, Russia	118:180,000	1:1525
1908	Rischbieth	London, England	39:67,945	1:1742
1919	Army Draftees	United States	1,466:2,510,791	1:1880
1924	Davis	Baltimore, Maryland	24:28,085	1:1170
1929	Peron	Paris, France	106:100,889	1:942
1931	Schroder	Munster, Germany	28:34,000	1:1214
1931	Gunter	Leipzig, Germany	102:102,834	1:1000
1933	Sanders	Holland	16:15,270	1:954
1934	Grothkopp	Hamburg, Germany	74:47,200	1:638
1934	Faltin	Finland		1:950
1934	Sanverero-Roselli	Italy		1:1000-1500
1939	Edberg	Goteburg, Sweden	28:27,000	1:960
1939	Fogh-Andersen	Copenhagen, Denmark	193:128,306	1:665
1940	Conway	New York	32:22,513	1:700
1940	Hendersen	Hawaii	35:18,024	1:550

Year	Author	Place	No. in Total Population	Incidence
1942	Grace	Pennsylvania	250:202,501	1:810
1944	Mueller	Wisconsin	736:567,504	1:770
1949	Hixon	Ontario, Canada	695:655,332	1:943
1950	Ivy	Pennsylvania	766:583,690	1:762
1951	Wallace	New York		1:1265
1953	Wallace	New York		1:1202
1954	Douglas	Tennessee		1:1694
1955	Ivy	Pennsylvania	1,592:1,201,976	1:754
1955	Lending	New York		1:1342
1957	Fogh-Andersen	Copenhagen, Denmark	644:393,457	1:754
1960	Sesgin-Stark	New York	21:27,087	1:1289
1960	Greene	California	2,185:1,765,746	1:808
1960	Greene	Hawaii	128:85,180	1:665
1960	Greene	Pennsylvania	1,446:1,242,408	1:859

Year	Author	Place	No. in Total Population	Incidence
1960	Greene	Wisconsin	692:485,104	1:701
1960	Rank	Tasmania, Australia		1:600
1961	Loretz	California	368:313,164	1:851
1961	Woolf	Utah	90:59,650	1:662
1961	Tretsven	Montana	229:123,144	1:538

Table III. Distribution of cleft lip, cleft lip and cleft palate, and isolated cleft palate cases by sex and by percent of total cases as reported in selected studies. (From Greene[46])

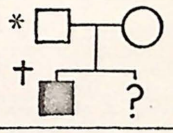
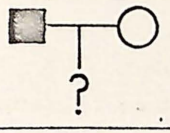
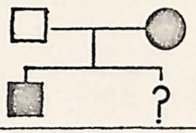
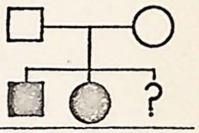
Malformation and study location	No. of Cases	% of Total cleft cases in study	Males No.	Males %
Cleft lip				
Ontario, Canada	195	30.8	127	65.1
Birmingham, England	66	23.2	40	60.6
California	102	27.8	61	59.8
Denmark	138	22.1	90	65.2
Pennsylvania	229	29.9	160	69.9
Lancaster, Pennsylvania	36	5.4	19	52.8
Montreal, Canada	14	13.7	6	42.9
London, England	93	20.4	61	65.6
Sub-Total	873		564	
Mean %		22.3		64.6
Cleft lip and cleft palate				
Ontario, Canada	316	49.8	199	63.0
Birmingham, England	105	36.8	62	59.0
California	155	42.1	90	58.1
Denmark	360	57.6	257	71.4
Pennsylvania	356	46.5	228	64.0
Lancaster, Pennsylvania	393	58.6	267	67.9
Montreal, Canada	56	54.9	37	66.1
London, England	152	33.3	103	67.8
Sub-Total	1,893		1,243	
Mean %		48.5		65.7
Isolated cleft palate				
Ontario, Canada	123	19.4	55	44.7
Birmingham, England	114	40.0	47	41.2
California	111	30.2	40	44.0
Denmark	127	20.3	43	33.9
Pennsylvania	181	23.6	69	38.1
Lancaster, Pennsylvania	242	36.1	103	42.6
Montreal, Canada	32	31.4	14	43.8
London, England	211	46.3	94	44.5
Sub-Total	1,141		465	
Mean %		29.9		40.8
Total	3,907		2,272	

Table IV. Incidence of oral-facial clefting in various syndromes.

Condition	Cleft lip and Cleft Palate	Isolated Cleft Palate
Acrocephalosyndactyly	--	25%
Arthromyodysplasia congenita	1%	--
Cleidocranial dysostosis	--	10%
Craniofacial dysostosis	--	20%
Glossopalatine Ankylosis	--	10%
Klippel-Feil syndrome	--	95%
Larsen's syndrome	--	95%
Mandibulo-facial dysostosis	--	up to 30%
Oculoauriculovertebral dysplasia	10%	--
Orodigitofacial dysostosis	*	*
Pierre Robin syndrome	--	75%
Trisomy D	75%	--
Trisomy E	1%	--

*Midline or lateral asymmetric clefts of palate in 75% of cases.

Table V. Recurrence risk figures for cleft lip and/or cleft palate offspring in which at least one affected individual has appeared in the immediate family.

Study	Affected family types					
Fogh-Andersen (1942)	Cleft lip Cleft palate	4.4%		2.0%	14.0%	--
	Isolated Cleft palate	1.8% 12.0%	‡{-H.D. +H.D.	7.0% +H.D.	17.0%	--
Curtis & Walker (1961)	Cleft lip Cleft palate	3.7%		4.0%	19.4%	--
	Isolated Cleft palate	2.5%		5.8%	14.3%	--
Curtis, Fraser & Warburton (1961)	Cleft lip Cleft palate	4.0% 3.6% 3.6%	-H.D. +H.D. §Con.	--	16.7%	9.0%
	Isolated Cleft palate	1.7% 7.2% 4.0%	-H.D. +H.D. Con.	--	15.4%	0.9%

* Normal individual
† Affected individual
} refer to Figure 4

‡ {-H.D. no previous familial history of clefting
{+H.D. previous familial history of clefting

§ Con. offspring resulting from a consanguineous marriage

Table VI. Segregation analysis* of the frequency of facial and oral discrepancies in relatives of probands with cleft lip and/or cleft palate.

Discrepancy	Parents and Siblings		Grandparents Aunts and Uncles		First Cousins		Double First Cousins		Total		Given No. of Involved Families
	N†	A‡	N	A	N	A	N	A	N	A	
Bifid uvula (a)	44	3	35	2	33	4	2	1	114	10	I, IV, V, VI, VII, XI
Mandibular lip pits	55	2	34	5	39	0	3	0	131	7	I, IX
Commissural lip pits	50	7	34	5	34	5	1	2	119	19	I, III, IV, VI, VII, VIII, XI
Notching of alveolus (a)	47	0	37	0	37	0	3	0	124	0	--
Raphe of upper lip (a)	46	1	36	1	37	0	3	0	122	2	V, VII
Asymmetrical nasal shape (a)	46	1	36	1	37	0	3	0	122	2	V, XI

Discrepancy	Parents and Siblings		Grandparents Aunts and Uncles		First Cousins		Double First Cousins		Total		Given No. of Involved Families
	N	A	N	A	N	A	N	A	N	A	
Malformed Maxillary Central and lateral incisors (a,b)	45	2	37	0	33	1	3	0	109	3	I, II, IV
Congenitally missing maxillary central and lateral incisors (a, b)	42	3	30	0	34	0	3	0	109	3	I, V, X
Excessive crowding of maxillary anterior segment (a,b)	43	2	26	4	33	1	3	0	105	7	I, III, XI

*Index cases are excluded in a segregation analysis using method of complete ascertainment

† Normal

ǂ Affected

(a) Cleft lip and cleft palate relatives were not included.

(b) Edentulous relatives were not included.

Table VII. Frequency of facial and oral discrepancies in relatives of probands with cleft lip and cleft palate when grouped together.

Group	Parents		Siblings		Individuals with more than one manifestation	Totals	
	N*	A†	N	A		N	A
Bifid uvula Commissural lip pits	32	4	39	25	4	71	29
Bifid uvula Cleft lip and cleft palate	40	8	56	36		96	44
Bifid uvula Cleft palate	20	2	26	15		46	17
Commissural lip pits Bifid uvula Cleft lip and cleft palate	45	6	41	31	6	86	37

* Normal
† Affected

Table VIII. Type of defect in relatives of probands with cleft lip and palate (CLP), cleft lip alone (CL), and cleft palate alone (CP).

Type of defect in the proband	Number of probands	Type of defect in affected relatives			
		CLP	CL	CP	Total Affecteds
CLP	8	8	3	9	25
CP	3	1	0	3	7

Table IX. Correlations between ocular and orbital measurements in both the control and relatives of probands in families with a history of clefting groups.

Variable	Innercanthal	Outercanthal	Occipital frontal circumference	Intercorneal	Canthal index	Circumference interorbital index	Skeletal interorbital
Innercanthal	1.000	0.656**	0.485**	0.688**	0.569**	0.846**	0.664**
Outercanthal		1.000	0.781**	0.885**	-0.205*	0.321**	0.810**
Occipital frontal circumference			1.000	0.743**	-0.170*	-0.001	0.664**
Intercorneal				1.000	-0.055	0.393**	0.845**
Canthal index					1.000	0.711**	-0.006
Circumference interorbital index						1.000	0.399**
Skeletal interorbital							1.000

* Correlation coefficient significant at the five percent level
** Correlation coefficient significant at the one percent level

Table X. Correlations between ocular and orbital measurements found in relatives of probands in families with a history of clefting.

Variable	Innercanthal	Outercanthal	Occipital frontal circumference	Intercorneal	Canthal index	Circumference interorbital circumference	Skeletal interorbital
Innercanthal	1.000	-0.596**	0.399**	0.667**	0.593**	0.850**	0.627**
Outercanthal		1.000	0.705**	0.856**	-0.237**	0.277**	0.774**
Occipital frontal circumference			1.000	0.685**	-0.170*	-0.100	0.586**
Intercorneal				1.000	-0.036	0.380**	0.797**
Canthal index					1.000	0.710**	-0.013
Circumference interorbital index						1.000	0.375**
Skeletal interorbital							1.000

* Correlation coefficient significant at the five percent level
** Correlation coefficient significant at the one percent level

Table XI. Mean scores of ocular and orbital distances in the control group.

Variable	Mean	Standard Deviation
Innercanthal	29.830 mm	± 3.02
Outercanthal	87.562 mm	± 7.41
Occipital-Frontal Circumference	532.621 mm	± 27.63
Intercorneal	43.697 mm	± 5.55
Canthal Index	34.124 mm	± 2.63
Circumference Interorbital Index	5.562 mm	± 0.46
Skeletal Interorbital	21.950 mm	± 3.11
Age	141.697 months	± 59.85

Table XII. Mean scores of ocular and orbital distances in the relatives of probands in families with a history of clefting.

Variable	Mean	Standard Deviation
Innercanthal	31.632 mm	± 3.00
Outercanthal	90.972 mm	± 6.55
Occipital-Frontal Circumference	538.815 mm	± 24.36
Intercorneal	47.165 mm	± 5.66
Canthal index	34.640	± 2.72
Circumference Interorbital Index	5.863	± 0.52
Skeletal Interorbital	23.447 mm	± 3.54
Age	281.240 months	± 20.77

Table XIII. Mean scores of combined ocular and orbital distances in the control and relatives of probands with a family history of clefting groups.

Variable	Mean	Standard Deviation
Innercanthal	30.916 mm	± 3.12
Outercanthal	89.622 mm	± 7.77
Occipital-Frontal Circumference	536.352 mm	± 25.81
Intercorneal	45.786 mm	± 5.85
Canthal Index	34.435	± 2.69
Circumference Interorbital Index	5.743	± 0.52
Skeletal Interorbital	22.852 mm	± 3.44
Age of both groups	225.759 months	± 17.89

Table XIV. Step-wise regression analysis on combined data with the control and relatives of probands in families with a history of clefting membership as the dependent variables and age, age squared, sex, ocular, and orbital distances as the independent variables.

Variable	Partial regression coefficient	Standard error of regress. coeff.	Amt. of dependent variation accounted for by each independent variables (%)	F	P
Sex	0.1119066	0.0680900	1.31	2.7037	NS
Age	0.0020300	0.0009300	14.66	4.7889	$<.01$
Canthal index	-0.0004070	4.0153000	0.67	4.0153	$<.05$
Circumference interorbital index	0.0000451	0.0000115	5.03	15.3896	$<.001$
Skeletal interorbital	-0.0003790	0.0001670	0.91	5.1120	$<.025$

Variable	Partial regression coefficient	Standard error of regress. coeff.	Amt. of dependent variation accounted for by each independent variables (%)	F	P
Age squared	-0.0000010	0.0000005	0.49	1.0228	NS
Innercanthal	NI*	-	1.22	0.0491	NS
Outercanthal	NI	-	-	0.0020	NS
Occipital frontal circumference	NI	-	-	0.0389	NS
Intercorneal	NI	-	-	0.0984	NS
		Total	24.29		

*not included in equation

XV. Step-wise regression analysis on the data of relatives of probands in families with a history of clefting with degree of relationship as the dependent variable and age, age squared, sex, ocular, and orbital measurements as the independent variables.

Variable	Partial regression	Standard error of regress. coeff.	F	P
Sex	NI*	-	0.317	NS
Age	NI	-	0.123	NS
Innercanthal	NI	-	0.009	NS
Outercanthal	NI	-	0.303	NS
Occipital-frontal circumference	NI	-	0.304	NS
Intercorneal	NI	-	0.279	NS
Canthal index	NI	-	0.573	NS
Circumference interorbital index	NI	-	0.245	NS
Skeletal interorbital	-0.000860	0.000726	1.401	NS
Age squared	NI	-	0.359	NS

*not included in equation

DISCUSSION

The review of the literature clearly demonstrates the complexities and problems encountered when attempting to study the etiologic aspects of cleft lip and cleft palate. Today, even with the vast knowledge available in the field of human genetics, a specific hereditary pattern for cleft lip and cleft palate has not been substantiated. The establishment of the etiologic factors responsible for cleft defects is one of the important problems that faces present day investigators.

In previous studies the relatives of individuals afflicted with cleft lip and/or cleft palate, except in pedigree studies, have been largely ignored in an investigation of this anomaly, and as a result, a variety of proposed modes of inheritance have been presented. It should be noted that the possibility of "carriers" for cleft lip and/or cleft palate in these pedigrees was never thoroughly explored. Recently, Fukahara and Saito[120] have demonstrated possible "microforms" or incomplete manifestations of cleft lip and cleft palate which may indicate or mark a gene carrier of this trait.

In searching for possible "microforms", a deliberately biased sample was used in the present study.

The relatives surveyed in this study were obtained only from families displaying a familial tendency for cleft lip and/or cleft palate. The selection of families for this study was based solely on the nearness of relationship of additional affected relatives to the proband. This includes affected siblings, parents, aunts, uncles, and first cousins. None of the studies[39,50,82] involving 200 or more family histories in which at least one child was affected with cleft lip and/or cleft palate were as critical in their selection. It was concluded by this investigator that the figures indicating the relative frequency of the "hereditary" family are of little or no value, when one considers a comparatively frequent affliction such as cleft lip and cleft palate, unless only the nearest relatives are included. Affected individuals not closely related to the proband may represent sporadic occurrences which are not the results of genes acting in a family. Thus, the 8.2 percent of families observed in the present study to demonstrate a familial occurrence for cleft lip and/or cleft palate may represent a more realistic figure than the 20 percent frequency alluded to in previous studies.

Results of the examination for various soft tissue discrepancies were found to be highly suggestive as a criteria for "gene carriers" in two families. One mother, who had an affected sibling (Family V), exhibited a raphé of the upper lip coincident with an extreme asymmetry of the nostril on the same side. The mother also displayed a very high palate, and overt hypertelorism which was confirmed by measurement. Furthermore, she bore two cleft lip and cleft palate children. Although no laminographic radiographs were taken to determine if midface bony defects were evident, this subject clinically resembled a number of patients presented by Fukahara and Saito[120] as gene carriers for the clefting trait. Interestingly, when considering the mother as an affected individual, the occurrence of a second child with cleft lip and cleft palate in this family was in accordance with risk figures of Fogh-Andersen[29] and Curtis[150] for an affected mother who already has one affected child. This finding seems to strengthen Fukahara and Saito's theory that individuals exhibiting specific alterations of the lip and palate may be gene carriers for cleft lip and cleft palate trait.

Since the minor facial and oral abnormalities

mentioned in this study were not observed in all expected instances, one must conclude that there may well be other significant oral-facial alterations which are manifestations of the clefting process than those observed in the present study.

An individual who was both the father and the uncle of children affected with cleft lip and cleft palate (Family XI) exhibited a gross asymmetry of the nares. A similar individual was described by Fukahara and Saito.[120] It was interesting to note that in Fukahara and Saito's subject, irregularities in the palatine bone and the nasal shelf were present.

After reviewing the literature, it was difficult for this investigator to believe that mandibular lip pits, cleft lip, and cleft palate were inherited independently of each other. The pedigree of Family I, strengthens the hypothesis of Van der Woude[47] and Curtis and Walker,[71] in that the triad of cleft lip, cleft palate, and mandibular lip pits may be due to a single dominant gene with variable expressivity. Furthermore, the severity of the clefts and lip pits, in Family I, increased in each Subsequent generation. This finding agreed with Van der Woude's conclusions. Baker[159] reported on a family in which mandibular lip

pits appeared as a single trait. In his study the degree of pitting varied in each individual, but an autosomal dominant hereditary pattern persisted.

Fogh-Andersen[29] and Fraser[24] have proposed that cleft lip with or without cleft palate appeared to be inherited separately from isolated cleft palate. In other words, if an individual had an isolated cleft palate, any affected relatives were much more likely to have an isolated cleft palate than to have a cleft lip with or without a cleft palate. Furthermore, both investigators suggested that in most cases cleft lip and cleft lip with cleft palate are due to the same gene. If one considers bifid uvula as a mild form of isolated cleft palate, the foregoing theories are supported in part with the data accumulated in the present study (Table VIII). In the families where the proband had cleft lip and cleft palate, the relatives were afflicted significantly more often ($p < .05$) with cleft lip and cleft palate than with isolated cleft palate. When families exhibited a proband with isolated cleft palate, the preponderance of isolated cleft palate to cleft lip with or without cleft palate in relatives was three to one.

If bifid uvula is a true manifestation of a

palatal cleft, it should follow the hereditary pattern of isolated cleft palate. Fogh-Andersen[29] and Fraser[24] have reported that isolated cleft palate is a simple autosomal dominant trait with limited penetrance and with some sex-limitation to the female. In this study, the combination of isolated cleft palate and bifid uvula produced an inheritance pattern which resembled that of an autosomal dominant gene with 50 percent penetrance. It should be noted, however, that only two of the 11 families studied exhibited a proband with isolated cleft palate.

The transmission of the bifid uvula trait contained no apparent sex-linkage or sex limitation. This does not agree with the proposed mode of genetic transmission of isolated cleft palate. Meskin and his associates[149] have proposed that as clefts of the palate become less severe, the apparent sex affinity for the female decreases; therefore, since bifid uvula is considered to be a mild manifestation of isolated cleft palate, the female sex predilection would be expected to be eliminated and this was observed here. However, the sample size in this study was quite small and further confirmation is

needed.

When bifid uvula and cleft lip with or without cleft palate were considered as a single trait, an autosomal dominant hereditary pattern was ascertained. If bifid uvula is considered a minor manifestation of isolated cleft palate and if the hereditary pattern of isolated cleft palate differs from that of cleft lip with or without cleft palate, the combination of bifid uvula with cleft lip with or without cleft palate, theortically, should not present a similar hereditary pattern. Therefore, this finding (autosomal dominant) further confuses the role of bifid uvula in cleft lip and/or cleft palate. One conceivable explanation is that the occurrence of bifid uvula may be due to the interaction of two or more genes and that no single mechanism can be accurately singled out.

Commissural lip pits, whose frequency was found to be similar to that of a select population, and which appeared to be occurring largely independent of the cleft lip and/or cleft palate condition, demonstrated an autosomal dominant pattern by itself. This result confirms Everett and Wescott's[129] findings.

Since the use of the selected oral and facial discrepancies as incomplete manifestations of cleft lip and/or cleft palate did not obviously present to this investigator a definite manner of inheritance for cleft lip and/or cleft palate, comparison of these results with other authors' proposed hereditary patterns of cleft lip and/or cleft palate is warranted.

The results of this study demonstrated that both cleft lip and/or cleft palate, in a small number of families (Families I, VII, VIII), exhibited autosomal dominance with varying degrees of penetrance. This finding is not in accord with the studies of Fogh-Andersen[29] and Fraser,[24] but does agree with Rank and Thomson's[67] observations.

In attempting to assign specific hereditary patterns to the accumulated data in this study, an autosomal dominant hypothesis was considered most likely with the aid of a contingent factor, penetrance.

As previously stated, penetrance is a concept which attempts to bridge the discrepancy between theortical expectation on the basis of a genetic hypothesis and actual observation. The concept of

penetrance is by nature a temporary, purely formal auxillary hypothesis without specific content, which is intended to make a genetic hypothesis acceptable. If the discrepancy between observation and expectation is considerable and its cause unknown, doubts about the hypothesis which was made the basis for the theoretical expectation are indicated. In this study, the concept of penetrance was used with a somewhat more exact meaning. Namely, it was used to explain the failure of appearance of certain oral-facial traits in some family members, who, on the basis of a genetic hypothesis, would be expected to show these traits.

The results of this study seem to imply that penetrance is not the property of the genes in question in cleft lip and/or cleft palate, but is a function of interaction with the rest of the genotype and of the environment.

The primary gene effect usually depends upon the action of a single pair of alleles, whereas numerous modifying genetic and exogenous factors are combined in secondary and tertiary effects. The concept of penetrance belongs in the realm of these secondary and tertiary complex gene effects,

but not in the realm of monomeric gene action. Thus, if it is said of a gene that it is dominant and has a penetrance of 50 percent, this means either that the effect of the gene depends on additional exogenous or genetic factors which are still unknown or that the complete expression of the gene action has not been recognized.

Accurate medical histories may be of some help in determining possible exogenous factors which may cause clefting. An excellent example was demonstrated in Family VIII; the proband's mother threatened abortion during a period in which development of the lip and palate was critical. Even with her husband exhibiting a cleft lip and cleft palate, the expression of the gene somehow may have been enhanced by this possible environmental factor.

The parent in Family III who was placed on thyroid medication poses an interesting question concerning the effect of altered endocrine function upon occurrence of congenital defects. The studies of Brown[45] and Henderson,[72] which both considered and then denied the possibility of thyroid deficiency as a teratogenic agent in congenital clefts, may be considered here.

The data concerning clinical and radiographic examination for interorbital distance yielded some most interesting results.

A number of investigators[142, 143] have observed individuals with cleft lip and cleft palate who exhibited hypertelorism. It has been suggested that the simultaneous occurrence of these anomalies indicated developmental retardation of the cranial facial structures. Most authors[141,142] agree that hypertelorism may be attributed to gross discrepancies in the growth pattern of the sphenoid bone.

One family (Figure 10) displayed overt hypertelorism among the parents and siblings and in this family the condition appeared to have a dominant mode of inheritance of its own, a condition already described by Bojlem and Brems.[146] However, this finding was an exception and, in fact, the data analysis actually showed that the canthal index and skeletal interorbital distances were significantly smaller in relatives of children affected with cleft lip and/or cleft palate. Since the raw data demonstrated greater values for the orbital and ocular measurements in the group of relatives of the proband with a familial history of clefting (Tables XI - XIII), mean values of the measurements were calculated

for the age range in which the ocular and orbital distances no longer increased with age. Even though the differences in the two groups were not found to be significant, the measurements in the group of relatives of a proband with a familial history of clefting were found to be slightly less. Therefore, the differences in ocular and orbital measurements noted in the raw data were most likely due to the mean age differences between the two groups. The meaning of these findings is not clear at this time, but if subsequent studies prove it to be a real one, it might ultimately provide a basis for selecting "gene carriers".

The significant differences in the ocular and orbital measurements between the two groups could not be related to the degree of relationship (siblings, parents, first cousins, and grandparents) to the proband, the true test of heritability. However, this failure may well have been due to the size of the population involved; therefore, it is suggested that additional measurements from individuals of new families with a history of clefting supplement these results before a final conclusion is attempted.

Assuming that "hypo" ocular and orbital distances

did occur in relatives of children affected with cleft lip and/or cleft palate, an explanation is very difficult.

It is noteworthy that hypotelorism has been previously reported to occur with median clefts of the face and palate.[160-162] Associated with these median clefts are the absence of the corpus callosum, agenesis of the prolabium, premaxilla and nasal bones, and microcephalia.

The developmental and anatomical discrepancies of hypotelorism include premature closure of the metopic suture with hypoplasia of the ethmoid region. These factors produce associated changes in the frontal bone and medial portions of the orbit. The orbits then assume an oval or egg shape with the longer axis extending upward and medially from the inferolateral margins. The medial orbital walls are almost vertical with loss of the usual medial convexity. No deviation of the medial convexity of the orbital wall from normal was apparent in the individuals included in the present study.

A theory which may be considered as conjecture on the author's part is that when relatives of the cleft child exhibit shorter ocular and orbital dis-

tances, and this phenotypic expression is transmitted genetically, polymorphic factors (whether they be environmental or genetic) attempt to correct for this anomaly by lateral growth of the midface. In doing so an overcorrection occurs, thereby preventing palatal closure. However, this does not explain the reason for clefting of the primary palate, that is, the lip and its associated structures.

In studying the etiologic aspects of cleft lip and cleft palate many problems, as brought out by this study, interfere with the progress of the geneticist in reaching definite conclusions. The key to the solution of these problems may eventually be found in families demonstrating a familial tendency for clefting. Envisioning the problems which have been encountered in this study, one can now realize the difficulty in reaching a conclusion as to the cause of clefting in the 189 "sporadic" cases which were referred to in portions of this work and were not studied.

SUMMARY AND CONCLUSIONS

The objective of this research was to attempt to provide information on the incomplete manifestations of a cleft lip and cleft palate "gene". An effort was made to determine how these incomplete manifestations might combine to produce an obvious mode of inheritance of a "clefting" gene in families with a history of cleft lip and cleft palate.

Parents of 206 children affected with cleft lip and/or cleft palate were questioned for any knowledge of individuals with cleft lip and/or cleft palate on either side of the family. Families were studied in which the criteria for their selection was based on the occurrence of at least one affected parent, sibling, or first cousin to the proband. A total of 11 families (138 individuals) were suitable for study.

Pedigrees of the selected families were constructed and analyzed for a specific hereditary pattern. Individuals within the families were examined for facial and oral discrepancies. The discrepancies included: bifid uvula, mandibular lip pits, commissural lip pits, raphé of the upper lip, notching of the alveolus, asymmetrical nasal shape (nares), congenitally malformed and missing maxillary

central and lateral incisors, and excessive crowding of the teeth in the anterior segment of the maxillary arch.

Examination for hypertelorism, which was considered to be indicative for abnormal midfacial growth, was completed on 100 relatives in families demonstrating a hereditary tendency for cleft lip and/or cleft palate. These measurements were compared with those obtained from 66 control individuals ranging from four to 22 years of age. A step-wise multiple regression analysis was used.

A questionaire concerning the history of the proband's mother during pregnancy was compiled and sent to the respective physicians. This was done in an attempt to eliminate possible environmental factors for clefting.

When selecting families with a hereditary disposition for cleft lip and/or cleft palate and when the coefficient of relationship was considered in order to eliminate sporadic occurrences of clefting, the following conclusions were drawn from this study: Raphé of the upper lip and asymmetrical nasal shape seemed to be, in individual families, valid criteria for determining possible "gene carriers" of cleft lip

and cleft palate. However, since these oral-facial abnormalities were not observed in all expected instances, significant facial manifestations other than those studied may have been present.

Mandibular lip pits, cleft lip, and cleft palate seem to be transmitted by a single autosomal dominant gene with variable expressivity. This observation, made on the single family in this study in which all three traits occurred simultaneously, confirms the observations of Van der Woude[47] and Curtis and Walker.[71]

Commissural lip pits appeared to be inherited independently of cleft lip and cleft palate and may be transmitted as an autosomal dominant trait.

The frequency of bifid uvula was much higher in relatives with a family history for clefting than in the general population. This result gives support to the findings of Meskin and his associates.[156]

No definite hereditary pattern for the condition of bifid uvula alone was found, and when bifid uvula and commissural lip pits were considered in various combinations with cleft lip and/or cleft palate no obvious validation of any manner of inheritance of the cleft lip and/or cleft palate condition was observed.

The circumference-interorbital index was significantly larger (p .001) in the relatives of the proband with a family history of clefting group. Skeletal interorbital distance and the canthal index was found to be significantly smaller in the relatives of the proband with a family history for clefting group (p .025 and p .05).

The significant differences in the ocular and orbital measurements between the two groups could not be related to the degree of relationship to the proband. This failure may well have been due to the size of the sample of the population involved and, therefore, it is suggested that additional measurements from individuals of new families with a history of clefting supplement these results before a final conclusion is drawn.

REFERENCES

1. Stern, Curt: Principles of Human Genetics. 2nd ed. San Francisco, W. H. Freeman Co., 1960.

2. Robinson, H. B.: Development of the face and oral cavity. In Sicher, Harry: Orban's Oral Histology and Embryology. 5th ed. St. Louis, C. V. Mosby Co., 1962, p. 15.

3. Bhaskar, S. N.: Synopsis of Oral Histology. St. Louis, C. V. Mosby Co., 1962.

4. Arey, B. L.: Developmental Anatomy. 6th ed. Philadelphia and London, W. B. Saunders, 1954.

5. Patten, B. M.: Human Embryology. 2nd ed. New York, McGraw-Hill, 1953.

6. Dursy, E.: Zur Entwicklungsgeschichte des Kopfes des Menschen und der Hoheren Wirbeltiere. Tübingen, H. Lauppschan, 1869.

7. His, W.: Unsere Koerperform und dos Physioligische Problem Ihrer Eutstohung. Leipzig, Verlag Von F.C.W. Vogel, 1874.

8. Stark, R. B. and Ehrmann, N. A.: The development of the center of the face with particular reference to surgical correction of bilateral cleft lip. Plast. Reconstr. Surg. 21:177, 1958.

9. Pohlman, E. H.: Die embryonale Metamorphose der Physiognomie und der Mundhohle des Katzenkophes. Dissertation, Leipzig, 1910.

10. Veau, Victor and Politzer, G.: Embryology of the harelip: the primary palate. Formation and anomalies. Ann. Anat. Path. 13:275, 1936.

11. Stark, R. B.: The pathogenesis of harelip and cleft palate. Plast. Reconstr. Surg. 13:20, 1954

12. Tondury, G.: Fortschritte der Kiefer und Gesichts Chirurgie. Stuttgart, Georg Theime Verlag, Teil 1, 1955.

13. Peter, Karl: Die Entwicklung des Saugetiergaumens. Ergebn. Anat. Entwicklungsgech 25:448, 1924.

14. Lazzaro, Carmelo: Sul mechanismo di chiusura del palato secondario. Monotore Zool. Ital. 51:249, 1940.

15. Walker, B. E. and Fraser, F. C.: Closure of the secondary palate in three strains of mice. J. Embryol. Exp. Morph. 4:176, 1956.

16. Zeiler, K. B., Weinstein, Samuel, and Gibson, R. D.: A study of the morphology and the time of closure of the palate in the albino rat. Arch. Oral Biol. 9:545, 1964.

17. Veau, Victor: Hasenscharten menschlicher Keimlinge auf der Stufe 21-23 mm. S. St. L. Z. Anat. Entwicklungsgesch. 108:459, 1938.

18. Millen, J. W.: Timing of human congenital malformation. Develop. Med. Child. Neurol. 5:343, 1963.

19. Fulton, J. T.: Closure of the human palate in embryo. Amer. J. Obstet. Gynec. 74:179, 1957.

20. Woo, Ju-Kung: Ossification and growth of the human maxilla, premaxillary and palate bone. Anat. Rec. 105:737, 1949.

21. Kraus, B. S.: Prenatal growth and morphology of the human palate. J. Dent. Res. 39:1177, 1960

22. Fleischmann, A.: Neue Erfahrungen über Gesichtsspalten bei Mensch und Tier. Sber. phy.-med. Soz. Erlangen. 69:315, 1937.

23. Hoepke, Hermann and Maurer, Hugo: Über die Bildung von Hassenscharten. Z. Anat. Entwicklungsgesch 108:768, 1938.

24. Fraser, F. C.: Thoughts on the etiology of clefts of the palate and lip. Acta Genet.(Basal). 5:358, 1955.

25. Fraser, F. C., Kalter, Harold, Walker, B. E., and Fainstat, T. D.: The experimental production of cleft palate with cortisone and other hormones. J. Cell. Comp. Physiol. 43(1):237, 1954.

26. Fitch, Naomi: An embryological analysis of two mutants in the house mouse both producing cleft palate. J. Exp. Zool. 136(2):329, 1957.

27. Walker, B. E. and Fraser, F. C.: Embryology of cortisone induced cleft palate. J. Embryol. Exp. Morph. 5(2):201, 1957.

28. Avery, J. K. and Devine, R. K.: The development of ossification centers in the face and palate of normal and cleft palate human embryos. Cleft Palate Bull. 9:25, 1959.

29. Fogh-Andersen, Poul: Incidence of Harelip and Cleft Palate. Copenhagen, Nyt, Nordisk Forlag, 1942.

30. Davis, J. S. and Ritchie, H. P.: Classification of congenital clefts of the lip and palate. J.A.M.A. 79:1323, 1922.

31. Sherman, H. M.: In Davis, J. S. and Ritchie, H. P: Classification of congenital clefts of the lip and palate. J.A.M.A. 79:1323, 1922.

32. Brophy, T. W.: Cleft Lip and Palate. Philadelphia, Blakiston Son and Co., 1923.

33. Veau, Victor: Division Palatine, Paris, Masson et Cie., 1931.

34. Dorrance, G. M.: The Operative Story of Cleft Palate. Philadelphia, W. B. Saunders Co., 1933.

35. Pruzansky, Samuel: Description, classification, and analysis of unoperated clefts of the lip and palate. Am. J. Orthodont. 39:590, 1953.

36. Kernahan, D. A. and Stark, R. B.: A new classification for clefts of the lip and palate. Plast. Reconstr. Surg. 22:435, 1958.

37. Harkins, C. S., Berlin, Asa, Harding, R. L., Longacre, J. J., and Snodgrass, R. M.: A classification of cleft lip and cleft palate. Plast. Reconstr. Surg. 29:31, 1962.

38. Davis, J. S.: The incidence of congenital clefts of the lip and palate. Ann. Surg. 80:363, 1924.

39. Sanders, J.: Inheritance of harelip and cleft palate. Genetica 15:433, 1934.

40. Krantz, H. C. and Henderson, F. M.: Relationship between maternal ancestry and incidence of cleft palate. J. Speech Hearing Dis. 12:267, 1947.

41. Hixon, E. H.: A study of the incidence of cleft lip and palate in Ontario. Canad. J. Public Health 42:508, 1951.

42. Gentry, J. T., Parkhurst, Elizabeth, and Bulin, G. V.: An epidemiological study of congenital malformations in New York State. Amer. J. Public Health 49:497, 1959.

43. MacMahon, Brian, and McKeown, Thomas: The incidence of harelip and cleft palate related to birth rank and maternal age. Amer. J. Hum. Genet. 5:176, 1953.

44. Ivy, R. H.: Congenital anomalies as recorded on birth certificates in the Division of Vital Statistics of the Pennsylvania Board of Health, for the period 1951-55 inclusive. Plast. Reconstr. Surg. 20:400, 1957.

45. Fogh-Andersen, Poul: Incidence of cleft lip and palate: constant or increasing? Acta Chir. Scand. 122:106, 1961.

46. Greene, J. C.: Epidemiology of congenital clefts of the lip and palate. Public Health Rep. 78:589.

47. Van der Woude, Anne: Fistula Labie Inferious Congenita and its association with cleft lip and palate. Amer. J. Hum. Genet. 6(2):244, 1954.

48. Loretz, Wayne, Westmoreland, W. W., and Richards, L. F.: A study of cleft lip and cleft palate births in California. Amer. J. Public Health 51:873, 1961.

49. Haug, Gustav: Statistical data on harelip based on 555 cases at V. Brums' Surgical Clinic at Tubingen. Beitr. Klin. Chir. 44:254, 1904.

50. Birkenfeld, Werner: Über die Erblichkeit der Lippenspalte und Gaumenspalte. Arch. Klin. Chir. 141:729, 1926.

51. Fortuyn, A.B. D.: Inheritance of harelip and cleft palate in man. Genetica 17:349, 1936.

52. Grace, L. G.: Frequency of occurrence of cleft palate and harelip. J. Dent. Res. 22:495, 1943.

53. Fraser, F. C. and Baxter, Hamilton: The familial distribution of congenital clefts of the lip and palate. Amer. J. Surg. 87:656, 1954.

54. Mazaheri, Mohammand: Statistical analysis of patients with congenital cleft lip and/or palate at the Lancaster Cleft Palate Clinic. Plast. Reconstr. Surg. 21:193, 1958.

55. Fraser, G. R. and Calnan, J. S.: Cleft lip and palate: seasonal incidence, birth weight, birth rank, sex, site, associated malformations and parental age; a statistical survey. Arch. Dis. Child. 36:420, 1961.

56. Woolf, C. H., Woolf, R. M., and Broadbent, R. T.: Genetic and non-genetic variables related to cleft lip and palate. Plast. Reconstr. Surg. 32:65, 1963.

57. Greene, J. C., Vermillion, J. R., Hay, Sylvia, Gibbens, S. F., Kerschbaum, Susan: Epidemiologic study of cleft lip and cleft palate in four states. J. Amer. Dent. Ass. 68:387, 1964.

58. Curtis, Elizabeth: Genetical and environmental factors in the etiology of cleft lip and palate. J. Canad. Dent. Ass. 23:576, 1957.

59. Test, A. R. and Falls, H. F.: Dominant inheritance of cleft lip and palate in five generations. Oral Surg. 5:292, 1947.

60. Sesgin, M. J. and Stark, R. B.: Incidence of congenital defects. Plast. Reconstr. Surg. 27:261, 1961.

61. Lutz, K. R. and Moor, F. B.: A study of factors in the occurrence of cleft palate. J. Speech Hearing Dis. 20:271, 1955.

62. Beder, O. E., Coe, H. E., Braafladt, R. P. and Houle, J. D.: Factors associated with congenital cleft lip and cleft palate in the Pacific Northwest. Oral Surg. 9:1267, 1956.

63. Neel, J. V.: A study of major congenital defects in Japanese infants. Amer. J. Hum. Genet. 10:398, 1958.

64. Tretsven, V. E.: Incidence of cleft lip and palate in Montana Indians. J. Speech Hearing Dis. 28:52, 1963.

65. McEvitt, W. G.: Cleft lip and palate and prenatal age. Plast. Reconstr. Surg. 10:77, 1952.

66. Peer, L. H., Strean, L. P., Walker, J. C., Bernhard, W. G., and Beck, G. C.: Study of 400 pregnancies with birth of cleft palate infants. Plast. Reconstr. Surg. 22:442, 1958.

67. Rank, B. K., and Thomson, J. A.: Cleft lip and palate in Tasmania. Med. J. Aust. 47:681, 1960.

68. Phair, G. M.: The Wisconsin cleft palate program. J. Speech Hearing Dis. 12:410, 1947.

69. Spriesterbach, D. C., Spriesterbach, Bette R., and Moll, K. L.: Incidence of clefts of the lip and palate in families with children with clefts and families without clefts. Plast. Reconstr. Surg. 29:392, 1962.

70. Fujino, Hiroshi, Tanaka, Katumi, and Sanui, Yoshihorn: Genetic study of cleft lips and cleft palates based upon 2,828 Japanese cases. Kyushu J. Med. Sci. 14:317, 1963.

71. Curtis, Elizabeth J. and Walker, N. F.: Etiological study of cleft lip and cleft palate. The Research Institute of the Hospital for Sick Children, University of Toronto, Toronto, Ottawa, 1961.

72. Henderson, Florence M.: Incidence of cleft palate in Hawaii. J. Speech Hearing Dis. 5:285, 1940.

73. Wallace, Helen M., Baumgartner, Leona, and Rich, Herbert: Congenital malformation and birth injuries in New York City. Pediatrics 12:525, 1953.

74. Stevenson, S. S., Worcester, Jane, and Rice, R. G.: 677 congenitally malformed infants and associated gestational characteristics: Parental factors. Pediatrics 6:208, 1950.

75. Kraus, B. S., Kitamura, Hironori, Ooe, Tadahiro: Malformations associated with cleft lip and palate in human embryos and fetuses. Amer. J. Obstet. Gynec. 86:321, 1963.

76. Trew, C. J.: Sisten plura exempla palati deficientis. In Fogh-Andersen, Poul: Incidence of Harelip and Cleft Palate. Copenhagen, Nyt. Nordisk Forlag, 1942, p. 49.

77. Lucas, J.: Remarks upon peculiarities in the human system apparently arising from disease before birth. Memoirs of the Medical Society of London 4:100, 1795.

78. Anna, F. J.: Beschreiburg und Abbildung eines Wolfs-rochens, Med. Chir. Zeit. 4:209, 1805.

79. Demarquay, J. N.: Quelques considérations sur le bec de lievre. Gaz. Med. Paris 13:52, 1845.

80. Murray, J. J.: Underscribed malformation of the lower lip occurring in four members of one family. Brit. For. Med. Chir. Rev. 26:502, 1860.

81. Rischbieth, H.: Harelip and cleft palate. In Fogh-Andersen, Poul: Inheritance of Harelip and Cleft Palate. Copenhagen, Nyt. Nordisk Forlag, 1942, p. 52.

82. Schroder, C. H.: Die Vererbung der Hasenscharte und Gaumenspalte. Arch. Rassenbiol. 25:369, 1931.

83. _____: Untersuchungen über die Vererbung der Hasenscharte und Gaumenspalte mit Besonderer Berucksichtigung des Erbgangs. Arch. Klin. Chir. 182:299, 1935.

84. _____: Erbliche Beziehungen der Hasenscharte und Gaumenspalte zu Anderen Körperlichen Missbildugen Insbesondere zu Wirbelsaulenmissbildungen. Beitr. Klin. Chir. 169:402, 1939.

85. Hantzschel, K.: Die eugenische Bedeutung der Angeborenen Spallbildungen. In Fogh-Andersen, Poul: Inheritance of Harelip and Cleft Palate. Copenhagen, Nyt. Nordisk Forlag, 1942, p. 56.

86. Cunningham, Bert: Inheritance of harelip. J. Hered. 15:370, 1942.

87. Cotterman, C. W. and Synder, L. H. Studies in human inheritance XVIII: The gene frequency analysis. Genetica 19:537, 1937.

88. Csik, L. and Mather, K.: The sex incidence of certain hereditary traits in man. Ann. Eugenics 8:126, 1938.

89. Mather, K. and Phillip, U.: The inheritance of harelip and cleft palate in man. Ann. Eugenics 10:403, 1940.

90. Schwartz, Ralph: Familial incidence of cleft palate. J. Speech Hearing Dis. 19:228, 1954.

91. Stiegler, E. J. and Berry, M. F.: A new look at the etiology of cleft palate. Plast. Reconstr. Surg. 21:52, 1958.

92. Idelburger, A. and Idelburger, K.: Serienmassige Zwillings Untersuchungen zur Erbpathologie den Lippen-Kiefer-Gaumenspalten. Z. Menschl. Vererb. Konstitutionl. 24:417, 1940.

93. Metrokos, J. D., Metrokos, Katherine, and Baxter, Hamilton: Clefts of the Lip and Palate in Twins. Plast. Reconstr. Surg. 22(2):109, 1958.

94. Douglas, Beverly: Deductions from the presence of cleft lip and palate in one of identical twins, from embryology and from animal experiments. Plast. Reconstr. Surg. 22:94, 1958.

95. Brown, Janet: Hypothyroidism as an etiology of cleft palate. J. Speech Hearing Dis. 3:247, 1939.

96. Campbell, D. K.: Anomalies of dentition suggestive of syphillitic heredity with cleft palate and harelip. J. Amer. Dent. Ass. 35:557, 1947.

97. Gregg, N. M.: Congenital cataract following German measles in the mother. Trans. Ophthal. Soc. Aust. 3:35, 1941.

98. Prendergast, J. J.: Congenital cataract and other anomalies following rubella in mothers during pregnancy. Arch. Ophthal. 35:39, 1946.

99. Swan, Charles and Tostevin, A. L.: Congenital abnormalities in infants following infectious diseases during pregnancy with special reference to rubella: a third series of cases. Med. J. Aust. 1:645, 1946.

100. Patrick, P. R.: Report of a survey of children born in 1941 with reference to congenital abnormalities arising from maternal rubella. Med. J. Aust. 1:421, 1948.

101. Brawner, D. L.: Maternal rubella: results following an epidemic. J. Med. Ass. Georgia 44:451, 1955.

102. Fraser, F. C.: Some experimental and clinical studies on the causes of congenital clefts of the palate and of the lip. Arch, Pediat. 77:151, 1960.

103. _____: Causes of congenital malformations in human beings. J. Chronic Dis. 10:97, 1959.

104. Isaacson, R. J. and Chaudhry, A. P.: Experimental induction of cleft palate with cortisone in inbred mice. J. Dent. Res. 40:732, 1961. (abstract)

105. Ingalls, T. H. and Curley, F. J.: Relation of hydrocortisone injections to cleft palate in mice. New Eng. J. Med. 256:1035, 1957.

106. Woolan, D. H. M. and Millen, J. W.: Effect of cortisone on the incidence of cleft palate induced by experimental hypervitaminosis. A. Brit. Med. J. 2:197, 1957.

107. Strean, L. P. and Peer, L. A.: Stress as an etiological factor in the development of cleft palate. Plast. Reconstr. Surg. 22:442, 1958.

108. Asling, E. W., Nelson, N. M., Dougherty, H. D., Wright, H. V., and Evans, H. M.: Development of cleft palate resulting from maternal pteroylglutamic (folic acid) acid deficiency during the latter half of gestation in rats. Surg. Gynec. Obstet. 111:19, 1960.

109. Peer, L. H., Bryan, W. H., Strean, L. P., Walker, J. C., Bernhard, W. G., and Peck, G. C.: Introduction of cleft palate in mice by cortisone and its reduction by vitamins. J. Int. Coll. Surg. 30:249, 1958.

110. Douglas, Beverly: Rose of environmental factors in the etiology of "so-called" congenital malformations. Plast. Reconstr. Surg. 22:214, 1958.

111. McGanity, W. J., Cannon, R. O., Bridgforth, E. B., Martin, Margaret P., Densen, P. M., Newbill, Josephine A., McClellan, G. S., Christie, Amos, Peterson, G. C., and Darby, W. J.: Effect of severe maternal dietary deficiency in causing intant deformities. Amer. J. Obstet. Gynec. 67:491, 1954.

112. Conway, Herbert: Effect of supplemental vitamin therapy on the limitation of incidence of cleft lip and cleft palate in humans. Plast. Reconstr. Surg. 22:450, 1958.

113. Pinsky, Leonard, and Fraser, F. C.: Congenital malformations after a two hour inactivation of nicotinamide in pregnant mice. Brit. Med. J. 2:195, 1960.

114. Warkany, Josef and Kalter, Harold: Experimental cleft palate interpretations and misinterpretations. Cleft Palate Bull. 7:9, 1957.

115. Warkany, Josef and Dereschle, F. M.: Congenital malformations induced in rats by maternal riboflavin deficiency: dentofacial changes. J. Amer. Dent. Ass. 51:139, 1955.

116. Warkany, Josef, Nelson, Rose C., and Shraffenberger, Elizabeth: Congenital malformations in rats by maternal nutritional deficiency. Amer. J. Dis. Child. 65:882, 1943.

117. Erdelyi, Robert: Influence of toxoplasmosis on the incidence of congenital facial malformations. Plast. Reconstr. Surg. 20:306, 1957.

118. Buchner, Franz: Origin of clefts in the maxillofacial region. Wien. Klin, Wschr. 71:145, 1959.

119. Feild, L. E., Kreshover, S. J., and Lieberman, J. E.: Effect of uterine circulatory arrest on the development of the rat fetus. J. Dent. Res. 39:657, 1960.

120. Fukahara, Tatsuo and Saito, Shinichi: Possible carrier status of hereditary cleft palate with cleft lip; report of cases. Bull. Tokyo Med. Dent. Univ. 10(2):333, 1963.

121. Lucas, R. C.: On the congenital absence of an upper lateral incisor tooth as a forerunner of harelip and cleft palate. Tr. Clin. Soc. 21:64, 1888.

122. Mengele, J.: Sippenuntersuchungen bei Lippen-Kiefer-Gaumenspalte. Z. Menschi. Vereb, Konstitutionsl. 23:17, 1939.

123. Davis, W. B.: Harelip and cleft palate. Ann. Surg. 87:536, 1928.

124. Bohn, Arne: Dental anomalies in harelip and cleft palate. Acta. Odont. Scand. 21(38):9, 1963.

125. Olin, W. H.: Dental anomalies in cleft lip and palate patients. Angle Orthodont. 34:119, 1964.

126. Gorlin, R. J. and Shapiro, Burt: Unpublished data. In Gorlin, R. J. and Pindborg, J. J.: Syndromes of the Head and Neck. New York, McGraw Hill, 1964.

127. Gorlin, R. J. and Pindborg, J. J.: Syndromes of the Head and Neck. New York, McGraw Hill, 1964.

128. Hall, D. C.: Report of a case of congenital pits of the lower lip associated with cleft palate. Dent. Pract. 14:227, 1964.

129. Everett, F. G. and Wescott, W. B.: Commissural lip pits. Oral Surg. 14:202, 1961.

130. Greig, D. M.: Hypertelorism. A hitherto undifferentiated congenital cranio-facial deformity. Edinburgh M. J. (New Ser.) 31:560, 1924.

131. Gross, Heinrich: Der Hypertelorismus. Ophthalmalogica (Basel) 131:137, 1956.

132. Fuller, R. W. and Weber, A. N.: Hypertelorism in association with chromatin sex abnormality in two siblings. Amer. J. Ment. Defic. 66:844, 1961-62.

133. Brown, Alexander, and Harper, R. K.: Craniofacial dysostosis: The significance of ocular hypertelorism. Quart. J. Med. (New Ser.) 15:171, 1946.

134. Goard, R. A.: Ocular hypertelorism of Greig: A congenital craniofacial deformity. Amer. J. Orthodont. 47:205, 1961.

135. Kersley, G. D.: Fragilitas ossium and allied conditions. St. Barth. Hosp. Rep. 68:159, 1935.

136. Posmer, Irving and Piatt, A. D.: Ocular hypertelorism with cleft palate and giant cell tumor. Radiology 35:79, 1940.

137. Vorisek, E. A.: Ocular hypertelorism of Greig. Amer. J. Ophthal. 24:928, 1941.

138. Van Bogaert, L. and Sweerts, J.: Sur l'hypertelorisme de Greig. J. belge de neurol. et de neurol. et de psychiat. 35:71, 1935.

139. Miur, D. C.: A case of hypertelorism. Brit. J. Child. Dis. 22:102, 1925.

140. Rawson, R. D. and Avila, E. G.: Hypertelorism. Rev. Especial. 5:372, 1930.

141. Isola, A.: In Arce, Manuel and Arce, Francisco: Roentgenographic study of craniofacial dysostosis. Amer. J. Roentgen. 47:275, 1942.

142. Aitchison, James: Hypertelorism as a diagnostic aid to dental anomalies. Dent. Rec. 73:311, 1953.

143. Drummond, W. B.: A case of hypertelorism. Arch. Dis. Child. 1:166, 1926.

144. Abernathy, D. A.: Hypertelorism in several generations. Arch. Dis. Child. 2:316, 1927.

145. Allen, F. M. D.: A case of hypertelorism without mental defect. Arch. Dis. Child. 1:171, 1926.

146. Bojlén, Krud and Brems, Toge: Hypertelorism (Greig). Acta Path. Microbiol. Scand. 15:217, 1938.

147. Berans, C.: Anomalies of the uvula. Philadelphia Med. Bull. 15:177, 1893.

148. McIntosh, Ruston, Merritt, K. K., Richards, M. R., Samuels, M. H., and Bellows, M. T.: The incidence of congenital malformations: A study of 5,964 pregnancies. Pediatrics 14:505, 1954.

149. Meskin, L. H., Gorlin, R. J., and Isaacson, R. J.: Abnormal morphology of the soft palate: The prevalence of cleft uvula. Cleft Palate J. 1:342, 1964.

150. Curtis, Elizabeth J., Fraser, F. C., and Warburton, Dorothy: Congenital cleft lip and palate. Amer. J. Dis. Child. 102:853, 1961.

151. Günther, H.: Hypertelorismus. Endokrinologie 13:61, 1933.

152. Currarino, Guido and Silverman, F. N.: Orbital Hypotelorism, arhinencephaly, and trigonocephaly. Radiology 74:206, 1960.

153. Jöhr, P. P. Tableaux de mensurations des distances oculares et craniennes. J. Hum. Genet. 2:247, 1953.

154. Baker, B. R.: Personnel Communication.

155. Brown, R. V.: Pattern and frequency of congenital absence of teeth. Iowa Dent. J. 43:60, 1957.

156. Meskin, L. H., Gorlin, R. J., and Isaacson, R. J.: Abnormal morphology of the soft palate: II. The genetics of cleft uvula. Cleft Palate J. 2:40, 1965.

157. Hansman, Charlotte F.: Growth of interorbital distance and skull thickness as observed in roentgenographic measurements. Radiology 86:73, 1966.

158. Li, J. C. R.: Statistical Inference II. The multiple regression and its ramifications. Ann Arbor, Edwards Brothers, 1964.

159. Baker, B. R.: Family with bilateral congenital pits of the inferior lip. Oral Surg. 18:494, 1964.

160. Gerald, B. E. and Silverman, F. N.: Normal and abnormal interorbital distances, with special reference to mongolism. Amer. J. Roentgen. 95:154, 1965.

161. Bell, W. E. and Van Allen, M. W.: Agenesis of corpus callosum with associated facial anomalies. Neurology 9:694, 1959.

162. Braitwaite, Fenton, and Watson, J., A report on three unusual cleft lips. Brit. J. Plast. Surg. 2:38, 1949.

CURRICULUM VITAE

Chester Tullio Coccia

September 17, 1935	Born, Detroit, Michigan
June 11, 1953	Graduated from Dearborn Fordson High School, Dearborn, Michigan
1953-1954	Attended Central Michigan College, Mount Pleasant, Michigan
June 18, 1957	B.S., University of Detroit, Detroit, Michigan
June 19, 1961	D.D.S., University of Detroit, Detroit, Michigan
August 5, 1961	Married Margaret Ann Eaves Detroit, Michigan
August 19, 1961- August 19, 1963	Captain, Dental Corps, United States Army
September 1, 1963- May 1, 1966	Graduate Student Post-Doctoral Research Fellow, Indiana University School of Dentistry

Professional Societies

American Dental Association
American Society of Dentistry for Children
American Academy of Pedodontics
Psi Omega, Professional Dental Fraternity

ABSTRACT

A STUDY OF THE HEREDITARY BASIS OF CLEFT LIP AND CLEFT PALATE By Chester Tullio Coccia

This study attempted to identify the incomplete manifestations of gene(s) producing cleft lip and/or cleft palate. An effort was made to determine how various oral-facial discrepancies, when considered as incomplete manifestations of clefting, might produce an obvious mode of inheritance of the clefting trait in families with a history of cleft lip and/or cleft palate. Eleven families were studied, selection being made on the basis of the degree of relationship of the affected individuals to the proband.

Oral and facial discrepancies including bifid uvula, mandibular lip pits, commissural lip pits, raphe of the upper lip, notching of the alveolus, asymmetrical nasal shape, congenitally missing and malformed maxillary central and lateral incisors, and excessive crowding of the teeth in the anterior segment of the maxillary arch were selected as possible incomplete manifestations of gene action. The results of this study demonstrated that when these manifestations were considered together with the cleft lip and/or cleft palate condition, no additional information on the manner of inheritance of the cleft lip and/or cleft palate trait was produced.

Ocular and orbital measurements, which may also be used in determining possible mid-facial discrepancies, were compared between the relatives of families with a history of clefting and a control group of individuals ranging from four to 22 years of age. A total of 166 individuals were compared. Significant differences in the circumference-interorbital index, skeletal interorbital distance, and the canthal index were found.

Since these significant differences in the ocular and orbital measurements could not be significantly related to the degree of relationship between affecteds (the test of heritability), they should be held with some reservation until a larger sample can be studied.